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PRESIDENT'S MESSAGE

Thanksgiving Day, 1948

TWO things have disturbed our members: first is the appeal for Federal Aid; second, the dictatorial manner in which the appeal for Federal Aid was presented.

1st. All must realize by now that there exists an acute financial situation in many medical schools. This has had the earnest thought of the Committee on Medical Education of the AMA and the deans of the Association of Medical Colleges who met just two weeks ago.

The educators are fully apprized of the reasons against such a move which would eventually mean the loss of their liberty and State Medicine; they realize that the Supreme Court has ruled that subsidies imply control; they know that Government operation is wasteful, inept and graft-ridden; they see the Army build unnecessary hospitals, the Navy, the Public Health Service and Veterans and some sub-departments likewise, and then they cry for more competent men to run ill-conceived and duplicating projects; they see full Army Camps open and unnecessary staffs on duty; they note the senseless unnecessary demand for more medical schools and for more medical students; they note government dispensaries are kept open—and to prove the need for their existence count every visitor that enters; they wonder how one could justify the purchase of a yacht for the study of fish and wildlife; they have not forgotten the WPA nor the relief measures for schools handled by Federal Agencies during the war; they have not forgotten the PWA, the NYC, The Lanham Act, the GI Bill and the CCC's; they know it will be more costly in taxes for any community to get funds through the Federal Government; they know that once they accept subsidies they cannot turn back; they feel that in the end one will have a "Police State," and we pediatricians will have a Pediatric W.P.A.

The deans of the Medical Colleges have seen this danger and they have adopted as their official policy the following taken from the Presidential Address of Dr. Walter Bloedorn—"Briefly summarized, these general principles which are basic to any sound program of financial aid for medical education from any source are: First, the acceptance by any medical school of any money from any source should in no way impose or imply any restriction of the freedom of the medical school in conducting its curricular

research, or administrative activities or in selecting its students. Second, the administration of funds for medical education should be free from political control. Third, decisions on grants to medical schools should be in the hands of medical educators."

The AMA have seen the dangers also and they are committed to raise funds for medical education.

Personally I don't want Federal Subsidies, and earnestly hope that the AMA can meet this issue by collecting funds.

2nd. Many members were annoyed at the action of the Executive Committee of the Academy, taken in June of this year—but this action was perfectly legal, though in my opinion not right, because it did not take into consideration the opinions of the members. On the other side it must be said that the Committee was faced with an emergency and acted in the best interest of the Academy. They faced a threat of social medicine. They now realize that they should have better educated members of the Academy. I feel strongly that in future decisions they will take the members into their confidence. I would even like to see them go further and in political economic questions poll individual members by mail ballot in the democratic way.

The Academy is in good financial status due to the untiring efforts of Drs. Grulee and Martmer. Dr. McCulloch has gotten our publication, PEDIATRICS, on its feet. The membership has increased. All things have blessed us.

JOHN A. TOOMEY

B. MUCOSUS CAPSULATUS (FRIEDLÄNDER) MENINGITIS; RECOVERY OF A THREE-WEEK-OLD INFANT TREATED WITH SULFADIAZINE AND STREPTOMYCIN

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BECAUSE of the rarity of B. mucosus capsulatus meningitis the case presented here may be of interest. It is the purpose of this paper to report B. mucosus capsulatus meningitis in a three-week-old infant who recovered, and to review the literature on the disease.

CASE REPORT

The patient was a white male infant three weeks of age. Three days before admission to the hospital, he became restless and nursed poorly. The next day he had six or eight yellow, loose, watery stools and fever.

On examination the baby kept his arms flexed and fists tightly clenched. Knee jerks were absent; fontanelle level. There was slight redness of the throat. Respirations were slightly rapid; breath sounds clear. Temperature was 38.5°C.

Spinal fluid was clear, showed six cells/cmm., negative Pandy, and no sugar by qualitative test. Several objects resembling encapsulated bacilli were seen.

In spite of the lack of definite evidence of meningitis, sulfadiazine was given orally, 120 mg./kg. body weight per day. The following morning, culture of the spinal fluid showed a luxuriant growth of white mucoid colonies which were elevated, rounded and often coalesced. Identification of B. mucosus capsulatus was made by the bacteriologist.

Streptomycin was then given subcutaneously every three hours in a dose of 50 mg. In addition, 25 mg. were given intrathecally each day. Sulfadiazine was administered according to the method of Hartmann[1] for treating severe types of meningitis.

There was little change in the child's condition, until the third day when he seemed to improve. Temperature was only slightly elevated and spinal fluid obtained the previous day had yielded no bacterial growth. Sulfadiazine determination showed 19.8 mg./100 cc. blood.

Clyses of sulfadiazine were discontinued (on the fourth day) and the drug given orally. Streptomycin was discontinued after four days of administration. The dose and frequency of sulfadiazine were gradually decreased and finally discontinued eight days after beginning treatment.

No spinal fluid could be obtained on a second lumbar puncture. The following day, only one drop of a thick viscid spinal fluid was obtained. Because it was believed that the child might die, streptomycin was administered intrathecally although it is bad technic to increase the volume of spinal fluid in cases of meningitis. This observation indicates the difficulty which may be encountered with B. mucosus capsulatus meningitis when the spinal fluid may be too thick to be obtained with an ordinary needle. After giving the streptomycin intrathecally, the lumbar puncture on the third day yielded a satisfactory amount of normal appearing spinal fluid.

HISTORY AND INCIDENCE OF THE DISEASE

B. mucosus capsulatus was discovered by Friedländer. Six years later Weichselbaum[2] reported a case of meningitis caused by B. mucosus capsulatus and proved its etiologic role. Since then, the organism has been found in many varied conditions—pneumonia, septicemia, periocarditis, endocarditis, peritonitis and osteomyelitis. The relatively frequent forms of Friedländer's infection with septicemia are rarely complicated by meningitis.

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Rothschild[3] reported a case which recovered. He found but one other case in the American literature, and this ended fatally. Ransmeier and Major[4] reported an analysis of a large series of cases from several cities which revealed that B. mucosus capsulatus was the causative organism in only three of 3,714 cases of meningitis. MacKay,[5] quoting Neal's[6] statistics, found six cases of meningitis due to this bacillus in a total of 3,599 cases. The greater portion of references concerning this infection are present in the European and Cuban literature. The exact incidence of Friedländer's meningitis is difficult to determine, for several reported cases do not give the bacteriologic data, and the clinical features of the disease show nothing pathognomonic. Mori[7] mentions 46 cases collected from the entire literature; whereas, Ransmeier and Major[4] were able to collect data on but 29 cases in 1943 in which the bacteriologic characteristics were sufficiently accurate to remove any doubt as to the cause of the meningitis. The incidence of meningitis due to B. mucosus capsulatus is extremely small, although the organism has been identified for the past 60 years.

Approximately half of all reported cases occurred in babies less than one year old. The patient whose case is reported here is the first in infancy known to recover. The other two patients who recovered were children over two years of age.

In discussing the organism, the term B. mucosus capsulatus should be the most satisfactory. The shape of the organism may vary greatly depending upon whether it is examined in pathologic exudates or on culture media. It appears generally as a diplobacillus or as a cocco-bacillus. It is gram-negative, non-motile, has a capsule which may show bipolar staining and has rather typical cultural findings. Growth is luxuriant on ordinary laboratory media. Colonies are whitish, glossy, rounded, elevated and often confluent. In removing a portion for microscopic examination it will be stringy, viscid and mucoid. There is good growth in sodium thioglycollate broth, and the organisms grow in lactose, dextrose, xylose, mannitol, maltose, and sucrose with fermentation and the production of acid and gas. There is no indole formation. A quelling test with A, B or C Friedländer's typing sera should be performed. Injection of the suspected organisms into mice should produce a fatal septicemia with recovery of organisms giving the cultural characteristics mentioned above.

To the 29 cases selected from the literature as having data sufficiently accurate to be termed B. mucosus capsulatus meningitis, Ransmeier and Major[4] have added their own patient; King's[8] patient, one by Mori,[7] another by Tartakoff[9] and that of the author are to be added. Ransmeier and Major[4] pointed out the two extremes of ages—infancy and beyond 40 years. Fourteen or almost 50% occurred during infancy, and more than half of this number developed in babies less than three months of age. Males predominate. Twenty-three males, eight females and three cases whose sexes were not stated are included. One was a Negro, two were Chinese and the remainder were white.

Portal of Entry and Predisposing Factors

Cases of B. mucosus capsulatus meningitis reported in adults usually have a probable source of primary infection, but this is not true for infants. In the adult patients, almost half of the reported cases listed chronic infections of the middle ear, mastoids or sinuses which yielded B. mucosus capsulatus. King[8] suggests the probable sources of infection leading to meningitis in his patient. Infants less than three months old, which account for half of all reported pediatric cases, have sinuses insufficiently developed to constitute such a problem. Infants may have debilitating diseases which render the body more

susceptible to a bacillus which is a habitual saprophyte. Congenital syphilis was present in the cases reported by Beitzke[10] and Papandrea.[11] Slobozianu[12] in discussing Friedländer's meningitis in the newborn presents two infants who also had intracranial hemorrhage.

Diagnosis

Adult patients have signs of meningitis; very young infants do not. In many of the reported cases, the diagnosis was made only extremely late in the course of the disease or at postmortem examination. There may be a few presenting symptoms, as in this case, or they may be entirely misleading as in the case reported by King.[8]

The diagnosis can be made only by bacteriologic examination of the spinal fluid. The fluid in this case was "normal" with the exception of finding large, broad, encapsulated rods which could be seen unstained. This "normalcy" of the spinal fluid is apparently not unusual, for Slobozianu[12] reported that a case had showed abnormal tension of the fontanelle with no abnormalities found in the spinal fluid. However, ventricular punctures yielded a seropurulent fluid with numerous B. mucosus capsulati. Slobozianu[12] also reported that Babonneix and Riom performed a lumbar puncture on an infant who had convulsions at the age of five days, and they obtained normal spinal fluid only to find very thick, fetid pus on doing a ventricular puncture. Tartakoff et al[9] reported a case of a 49-year-old man in whom the spinal fluid became increasingly gelatinous to the point where only drops could be obtained even by suction. After the administration of streptomycin, this thick fluid became aqueous. According to Ransmeier and Major[4] approximately one-fourth of the direct smears made from the fluid obtained on the first lumbar puncture may be negative. If so, a meningococcal meningitis may be erroneously suspected. Occasionally petechial or ecchymotic areas of the skin may appear if there is a B. mucosus capsulatus septicemia, further suggesting a meningococcal infection.

The abnormal spinal fluid shows the usual increased number of cells with polynuclear leukocytes predominating, a decrease in the sugar content of the fluid, a positive Pandy test and an increased protein content. Thus the differential diagnosis depends entirely upon finding the organism either in smears or on culture with further bacteriologic identification.

Prognosis

The age of patients who have B. mucosus capsulatus meningitis is of great prognostic importance. Early infancy and old age are the periods of highest mortality. A septicemia is serious; and, if the meningitis is secondary to such a blood infection, the disease is apparently always fatal although modern methods of treatment may alter this. As summarized by Ransmeier and Major,[4] 10 patients had blood cultures, five of which were positive. Those patients having positive blood cultures all died. Of the remainder who had negative blood cultures, two survived, while the third, a 17-day-old infant reported by Elias,[13] apparently was recovering when he died in an outbreak of "influenzal pneumonia." The other two patients died of meningitis although the first received sulfadiazine.

Rothschild[3] reviewed the literature in 1931 and stated that there had been three recoveries previous to his patient. However, the case reported by him is apparently the first nonfatal case of meningitis due to B. mucosus capsulatus which had adequate bacteriologic data to substantiate such a diagnosis, and recovery of this patient followed surgical drainage of a subdural abscess. Since then, there have been only three patients of pediatric age who have lived. These are: a 26-month-old boy reported by Mori,[7] Montes

and Real's[14] patient who was a boy two years of age, and the infant reported in this paper who was three weeks old.

It is evident then that sulfonamide compounds offer hope for a cure in this fatal disease. Our patient was also treated with streptomycin, and this drug promises to alter further the mortality statistics.

Treatment

There are several reports of the use of sulfonamides in Friedländer infections.[4, 7, 8, 14–17] Two of these have been successful; whereas, the patients of Ransmeier and Major[4] and of King[8] died. In attempting to evaluate the use of the drug, it is significant that in the latter two cases the diagnosis was not made early. The failure of sulfonamides to effect a cure in other types of meningitis when used relatively late in the course of the disease is well known. However, this drug remains extremely valuable. In 1938, Brown[15] reported a case of chronic pulmonary disease due to B. mucosus capsulatus which he treated with sulfanilamide and concluded that the drug was a "specific for Friedländer's bacillus." But in the same year, Gross et al[16] wrote that the efficacy of sulfonamide therapy against Friedländer infections in mice was still open to question. As newer sulfonamides were developed, these too were evaluated, and in 1943 Sesler and Schmidt[17] carried out an investigation to determine the relative action of various sulfonamides against infections with different strains of B. mucosus capsulatus. They concluded that sulfadiazine and sulfapyrazine were the two most active of this group of drugs although various strains of the bacillus possessed different degrees of responsiveness. Sulfadiazine is given in large quantities with the solution providing sufficient alkalinizing agents and promoting urinary excretion.

All reports of the use of streptomycin state that the drug is effective in Friedländer infections. Heilman et al[18, 19] reported that, following the administration of streptomycin intramuscularly in patients not having meningitis, no streptomycin could be found in the spinal fluid. In a second study, in which the drug was administered to several patients with meningeal infection, these authors concluded that in the presence of meningitis, concentrations of streptomycin in the spinal fluid approximately one-fifth that in the blood could be found after intramuscular administration. And, if the drug was given intrathecally, bactericidal amounts were found for at least 24 hours after the injection. Buggs et al[20] reached the conclusion, ". . . streptomycin may penetrate into the cerebrospinal fluid after systemic injection if the meninges are inflamed." This fact seems to be especially important in treating meningitis due to B. mucosus capsulatus as often the infection is severe and the spinal fluid is almost gelatinous. In the case reported in this paper, 25 mg. were given intrathecally each 24 hours when possible. Every three hours 50 mg. of streptomycin were given subcutaneously. It is presumed that one of the chief factors in this patient's rapid recovery must be streptomycin.

Heat, oxygen, respiratory stimulants and sedatives to control convulsions are all employed if indicated.

Summary

B. mucosus capsulatus (Friendländer) meningitis has been a disease entity for approximately 60 years. It occurs chiefly in very young or aged males. The diagnosis in the pediatric age group is especially difficult because of the paucity of symptoms and physical findings referable to the central nervous system or of any primary source of infection.

The meningitis differs from other types in that the spinal fluid becomes almost gelatinous unless treatment is quickly employed. Less than 50 cases of B. mucosus capsulatus meningitis have been reported, and only five of these have recovered. With the use of streptomycin and sulfadiazine, the mortality rate may be greatly reduced if the cases are diagnosed and treated early in the course of the illness.

A case of B. mucosus capsulatus meningitis occurring in a three-week-old male infant who recovered has been presented.

Acknowledgement

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SPANISH ABSTRACT

Meningitis B. Mucosus Capsulatus (Friedländer); Restablecimiento de un Infante Tratado con Sulfadiazina y Estreptomicina.

Se relata un caso de un infante de tres semanas con meningitis que mostró B. mucosus capsulatus en el cultivo del flúido espinal. El restablecimiento vino después de un tratamiento con sulfadiazina y estreptomicina.

Talvez la mayor dificultad que se ha encontrado en meningitis B. mucosus capsulatus es en la diagnosis. El paciente adulto usualmente tiene una fuente fundamental de infección, lo que no sucede en el infante. Por regla general no hay síntomas que indiquen complicación del sistema central nervioso, a pesar de la marcada enfermedad del paciente. Aproximadamente una cuarta parte de los primeros exámenes del flúido espinal en casos conocidos, se han clasificado como normales. Es imperativo que se haga un examen del flúido espinal cuanto antes, porque pueda ser imposible obtener flúido espinal después de que el niño haya estado enfermo varios días.

El tratamiento consiste en la adecuada administración de la sulfadiazina y la estreptomicina. El problema que todavía no se ha resuelto es si la estroptomicina debe administrarse intratecalmente. Pero hasta que hayan más pruebas en contra parece prudente introducir la estreptomicina en el conducto vertebral. Una diagnosis a tiempo y un tratamiento adecuado con sulfadiazina y estreptomicina darán por resultado el restablecimiento.

115 S. Union St.

THE ETIOLOGY OF EKIRI, A HIGHLY FATAL DISEASE OF JAPANESE CHILDREN

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CLINICAL AND BACTERIOLOGIC STUDIES

EKIRI is a highly fatal disease of Japanese children in the age group of two to six years, which is prevalent in the summer season. In 1939 more than 30,000 cases and more than 15,000 deaths from the disease were reported in Japan. The incidence varies somewhat from year to year but is consistently high and the death rate is always between 30% and 60%. The disease has been extensively studied by Japanese workers and much written in their journals concerning symptomatology, laboratory findings, pathology and possible etiology. Clinically Ekiri is characterized by sudden onset with high fever, diarrhea, vomiting and convulsions. The course is short, death occurring in four to 48 hours. Children surviving the first 48 hours usually recover after a variable period of convalescence.[1] Bacteriologic studies have yielded dystentery bacilli from the stools of about half the patients; S. sonnei being most often found, the S. of Flexner and S. ambigua less often, whereas the supposedly more toxic S. dysenteriae is almost never isolated. At postmorten examination pathologic changes are either conspicuous by their absence or compatible with early bacillary dysentery. The high fatality rate, the predominance of convulsions, the extreme fever and the failure to isolate dysentery bacilli in many typical cases of Ekiri suggested that the disease was not dysentery or that some additional factor was involved. The Japanese considered many possibilities: that a peculiarity of the constitution of Japanese children led them to react differently from children elsewhere, the old concept of status thymicolymphaticus often being evoked; that infection by an unknown agent perhaps some type of colon bacillus, perhaps a virus either acting alone or in conjunction with dysentery bacilli was the cause of the disease; that there was some obscure toxin formed by dysentery bacilli in Japan or by dysentery infection in Japanese children which led to the peculiar and serious manifestations of Ekiri. They looked for excess amounts of histamine, studied the effects of histamine and guanidine administration to animals, looked for excess ammonia in the blood of patients but could find nothing to explain either the serious symptoms of Ekiri or why the disease was practically limited to the age group of two to six years.

For treatment the main reliance was always placed on the elimination of possible toxins from the gastro-intestinal tract. Large and repeated doses of castor oil were followed by glycerine and water enemata. Because most physicians felt that the heart

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was severely affected, "cardiotonics," camphor, caffein, digitalis and even strychnine were used. Recently at some hospitals sulfonamides had been given with apparent slight beneficial results. Parenteral fluid therapy, always in small amounts, had also been used to some advantage.

Bacillary dysentery is common in Japan during the hot summer season. In 1939 60,000 cases of dysentery were reported with 5,000 deaths. If one includes Ekiri as dysentery, there were 90,000 cases with 20,000 deaths and the majority of the deaths occurred in the age group of two to six years with the fulminating symptoms of Ekiri.

One may find in the American and European literature occasional reports of one or two cases of bacillary dysentery in small children with symptoms similar to those seen in Ekiri. Hardy and Watt[2] present one such case of a seven-year-old Negro boy in Louisiana and mention that they have seen other similar cases in infants and younger children which stand clearly apart from the usual clinical types of dysentery. They state that convulsions often occur in these patients and that there is a marked contrast between the minor demonstrable anatomic changes in the colon found on postmortem examination and the clinical signs and symptoms. A notable feature of the cases is the degree of cerebral edema as shown by the increased weight of the brain, flattened convolutions and a pressure cone about the inferior surface of the medulla. A recent report by Hardy and Watt[3] on 438 cases of dysentery, as seen in endemic areas in Georgia and New Mexico in 1937 and 1940 before the days of sulfonamide therapy, will serve to illustrate the more common picture of dysentery infection as seen in the United States. The disease was severe only in infants; mild in older children and adults. Only 39 deaths were recorded, none in patients over two years of age. Death seldom occurred in the first five days of illness but in the second or third week from dehydration, malnutrition or secondary infection. Convulsions were seen in less than 3% of the patients. It is no wonder that the Japanese could not reconcile this picture with the Ekiri they so greatly feared in their children.

In the summer of 1947 under the auspices of the Japanese Institute of Health and the Public Health and Welfare Section of SCAP (Supreme Command of the Allied Forces) a study of Ekiri was carried out by a team consisting of a clinician, a bacteriologist and pathologist, and a biochemist. Cases of Ekiri were reported to us as they were admitted to the five municipal contagious disease hospitals in Tokyo. With the aid of the Japanese physicians we were able to secure clinical histories, examine the patients, obtain fecal matter and blood for culture and for chemical determinations and to examine pathologic material postmortem.

The clinical history of Ekiri was that described in many Japanese articles. Children of two to six years became suddenly ill with high fever, often 40.5°C. or more, diarrhea which was usually bloody, vomiting, extreme lethargy alternating with irritability, yawning spells and convulsions which occurred some hours after the onset of other symptoms.

On examination we found the children lying quietly in bed, often semicomatose. The muscles of the face looked stiff, the eye slits narrow, both because of periorbital edema and spasm of the periorbital muscles. There was pursing and curving of the lips with trismus on crying. Spontaneous twitching of the muscles of the face, neck and extremities was often visible. Some of the children were flushed, some very pale, a few had urticaria. Although there was evidence of general dehydration, edema was present over the backs of the hands and the tops of the feet and sometimes the shins. The children were hyper-

ventilating, the chest was over-expanded, the respirations often grunting with difficulty in expiration. The abdomen was usually distended, often with marked peristaltic patterns visible. When the child was aroused he looked confused and at times seemed delirious. He complained of pain when his extremities were handled. When the legs were raised and gentle pressure applied above or below the knee the extremity became stiff, the foot extended and turned inward, and the toes often jerked. On closer examination we found that the pupils were often widely dilated or contracted and reacted poorly to light. There might be strabismus or nystagmus or both. The heart beat was extremely rapid, the cardiac sounds loud, the pulse full and bounding with high pulse pressure. Often a pistol shot sound could be heard over the femoral artery. Although it was difficult to obtain the deep reflexes because of muscle spasm, some were increased; often they were greatly diminished or absent. When fluids were offered the child might drink thirstily, only to vomit projectilly a few minutes later. The vomitus often contained coffee ground material.

An occasional child was even more rigid than those described or became so on handling. He had a clonic convulsion or a tonic spasm. He might go into extreme opisthotonos, and his chest would become fixed in inspiration with the muscles so tightly contracted that attempts at artificial respiration proved fruitless. The body remained in rigor mortis after death.

If the child survived the early stage of the disease and began to improve the temperature fell, diarrhea diminished or ceased, vomiting stopped and the muscles tended to relax. At this stage the classical signs of tetany, positive Chvostek, Trousseau and peroneal sign could be elicited with ease. Such rapid disappearance of acute symptoms sometimes took place even in children who had earlier seemed desperately ill.

Other children, as their illness progressed became more deeply comatose. The temperature might fall or rise to 41.0° or 42.0°C. They relaxed or more often went into a kind of decerebrate rigidity. Respirations became deep and pauseless as in severe salicylate intoxication or were Biot or Cheyne-Stokes in type. Strabismus and nystagmus were marked. Although the heart beat was still strong, the pulse finally became weak or imperceptible and the veins seemed empty. The child was pale or cyanotic. Frequent convulsions might continue or ceaseless athetoid movements occur. We thought that such children were suffering from peripheral circulatory collapse with anoxia of the brain.

We soon began to examine the children who were considered to have dysentery rather than Ekiri. They also had signs of tetany, good peripheral signs but less marked cerebral and autonomic nervous system signs. Almost all of these children recovered in a few days, often without specific therapy. An occasional child developed a chronic dysentery with malnutrition and sometimes severe hemorrhage from the bowel. The outstanding difference between the two groups seemed to be the severity of the tetany, rather than the severity of the dysentery infection. A few children had tetany with what appeared to be a non-specific gastro-enteritis rather than dysentery. The stools did not contain pus or blood and tended to be more watery.

The serum calcium of the children was determined and found to be low and we began to treat the patients with calcium. Because of the severity of the tetanic manifestations and the vomiting calcium chloride was used intravenously. The effects in the early cases were spectacular. When the child had received about 5 cc. of a 10% solution of calcium chloride he began to lick his lips, coughed a time or two, cried and then relaxed.

He drew up his legs, moved his arms, turned over in bed, seemed surprised that he could move so easily again and went off into a peaceful sleep. Repeated administration of calcium would hold the tetany in check and allow some children with Ekiri to recover. However, during the illness most of the children had become dehydrated from high fever, hyperventilation, muscle spasm and convulsions. The physicians in the Tokyo hospitals were giving only 300 cc. of fluid at best and often none at all. If we were to save the children, it was necessary to persuade the physician to increase fluid therapy greatly, up to 1000 cc. or more of fluid a day. To this therapy we added sodium sulfathiazole, the only sulfonamide available in Japan for parenteral use. Toward the end of our stay when all these measures, calcium, sufficient fluids and sulfathiazole could occasionally be given early we were able to save children for whom the attending physician had given a hopeless prognosis. With calcium therapy even in late cases marked temporary improvement in hyperventilation, muscular rigidity, twitchings and convulsions were often seen but signs of central nervous system involvement and circulatory collapse remained and the child did not get well.

In the course of the summer cultures were made from the stools of 106 patients. Approximately two-thirds of the patients were considered to have Ekiri and one-third dysentery. Of 106 stool cultures 95 were positive for dysentery bacilli, 11 negative. Forty-two of the dysentery bacilli were found to be S. sonnei, 32 S. of Flexner, 20 S. ambigua, 1 S. dysenteriae. Of the 11 patients from whom no dysentery organisms were isolated five had dysentery according to clinical criteria and six showed no clinical evidence of dysentery infection. For stool cultures S.S. medium was employed and large inocula used. The fact that the Japanese use only Endos' medium for culture and usually inoculate with a small amount of stool seemed the probable explanation of their failure to obtain positive stool cultures in many cases. Thirteen blood cultures were obtained on patients who were severely ill and all proved negative. Thirteen attempts to isolate a virus by scarification and inoculation of fecal material on a rabbit's cornea produced no positive results.

Postmortem examination was performed on 29 children. The gross pathologic changes found in 24 were those of bacillary dysentery. In the majority of cases the changes were mild. There was edema of the colon, slight ulceration without the formation of false membrane and no extension of the lesion into the small bowel. In some instances, especially the cases seen late in the summer, the dysentery was apparently severe enough to account for the death of the patient, even had there been no complicating tetany. Since the Japanese death rate from dysentery alone is high and their food habits make it probable that they often ingest large doses of dysentery bacilli, one would expect severe infection at times. Examination of organs other than the colon revealed cloudy swelling. The lungs were emphysematous and sometimes edematous with subpleural hemorrhage and occasional hemorrhages into the alveoli. There was congestion and bleeding of the gastric mucosa. The brains were edematous and heavy with flattening of the convolutions and much subpial edema. The hearts, concerning which the Japanese had been greatly worried, were normal in every case. Twenty-two positive cultures were obtained from the colon; seven each were S. sonnei, S. of Flexner and S. ambigua, and one the S. dysenteriae bacillus. One stool culture proved negative in spite of gross evidence of dysentery and one colon was not cultured. Of the five patients in whom no evidence of dysentery was found, one had pneumonia, one cystitis; in the other three no evidence of infection and no obvious cause of death was found. Microscopic sections of tissues have not as yet been examined.

Chemical and Nutritional Aspects

From the clinical observations three disturbances of body function emerged to the foreground. They were: tetany, hyperventilation, and dehydration. The chemical studies were in the main directed to elucidating the mechanism of these disturbances. Later, when the question of underlying nutritional deficiencies engaged our interest, an orienting study on a small group of control Japanese children was carried out, directed to assessing these factors. The data to be reported are preliminary and fragmentary, and need to be greatly amplified in many directions. Limitations in time of stay and difficulties connected with the setting up of a laboratory in a foreign country impoverished by war and destruction in some measure excuse the deficiencies in our work. Without the enthusiastic and capable help of the Japanese colleagues in the laboratory little if anything could have been accomplished.

TABLE I

Distribution of Serum Calcium Values in 75 Patients

Diagnosis	Ca mg. %					Total no. of values
	<7	7 to 8	8 to 9	9 to 10	>10	
Ekiri	4	12	13	5	0	34
Dysentery	0	2	17	18	4	41

In Table I are summarized the data on serum calcium of 75 patients whom we had occasion to study before institution of calcium or fluid therapy. It may be seen that of 34 patients with Ekiri, 16 (almost one-half) had calcium values below 8, and 13 between 8 and 9 mg./100 cc. serum; whereas, of 41 dysentery patients, with as a rule much less severe tetany, only two had calcium values below 8 mg./100 cc. serum. Most of these patients had moderate decreases of calcium and only four had values above 10 mg./100 cc. serum.

Tables II, III and IV deal with the studies of the CO_2-pH equilibrium. Table II shows data on the CO_2 content of the serum of 17 patients. It may be seen that moderately decreased values were commonly observed, but that extremely low values were uncommon. A conclusion that these data are indicative of an acidosis is unwarranted as is shown by the data in Table III, in which the serum pH values are grouped. It is evident that the bulk of the values were distributed in the normal range. No value below 7.25 was ever observed. It should be emphasized that these data were determined on venous blood. Many of the patients had poor venous return and some were in circulatory collapse. Under such conditions with increased accumulation of CO_2 and lactic acid and depletion of oxygen in the venous blood, arteriovenous differences increase greatly beyond the normal range. One may infer with certainty that the pH values on the arterial blood were considerably higher, perhaps on the average by as much as 0.2 pH units, than those depicted. In Table IV are shown the values for the CO_2 tension, which reflects in an objective manner the ventilation of the lungs. As the ventilation of the lung increases, the CO_2 tension in the alveoli and therefore in the arterial blood, decreases. The CO_2 tension in the venous blood is normally about 46 mm.; that is, 6 mm. higher than in the arterial blood. The data indicate a marked decrease of the CO_2 tension below the normal in all cases.

Again it must be remembered that these values were determined on venous blood and that the CO_2 tension in arterial blood and therefore in the lungs must have been lower. But even taken at face value the figures give evidence of an extreme degree of hyperventilation. One may summarize the evidence of Tables II to IV by stating that it favors the assumption of a primary hyperventilation with respiratory alkalosis, with compensation or rather complication by the development of a secondary acidosis of the anoxic type, perhaps with lactic acid accumulation. A few determinations of blood lactic acid were carried out and showed increased values in some of the severe cases.

TABLE II

DISTRIBUTION OF SERUM CO_2 VALUES IN VENOUS BLOOD OF EKIRI PATIENTS

CO_2 content (normal 24–30) mEq./l					Total no. of values
<12	12 to 15	15 to 18	18 to 21	21 to 24	
3	3	2	5	4	17

TABLE III

DISTRIBUTION OF SERUM pH VALUES IN VENOUS BLOOD OF EKIRI PATIENTS

pH (normal 7.35–7.45)					Total no. of values
7.25 to 7.30	7.30 to 7.35	7.35 to 7.40	7.40 to 7.45	>7.45	
2	4	6	7	1	19

TABLE IV

DISTRIBUTION OF SERUM pCO_2 VALUES IN VENOUS BLOOD OF EKIRI PATIENTS

pCO_2 (normal 46) mm. Hg.					Total no. of values
<15	15 to 20	20 to 25	25 to 30	30 to 35	
1	2	3	3	8	17

An elevated NPN was determined to be the chemical correlate of the clinically evident dehydration. Illustrative data are shown in Table V where calcium and NPN values of several fatal cases of Ekiri are listed. The degree of NPN retention was impressive in view of the common history of illness of few hours' duration and the relative mildness of the diarrhea. The increases give evidence of a rapidly progressive water loss, mostly by way of the lungs, caused by the extreme hyperventilation and fever, in addition to the losses of electrolyte-containing fluid with vomitus and diarrheal stools.

From these data a hypothetical picture of some complexity may be drawn, in which a preexisting tendency to hypocalcemic tetany is given a leading role. The tetany, made

manifest by infection, is thought to be the basis of the unusual degrees of hyperventilation and fever observed which were often entirely out of keeping with the severity of the infection. An increased irritability of the respiratory center has been demonstrated in infants with tetany.[4] On the other hand hyperventilation is known to be a powerful influence capable of transforming latent tetany to its manifest form.[5] Additional causes of fever and hyperventilation in the patient may be sought in an increased heat production, brought on by the infection *per se* and by the activity of the tetanic muscles, as well as in a decreased dissipation of heat, caused by impairment of circulation and decrease of blood volume resulting from water loss. The water loss in part is caused by loss of gastro-intestinal secretions; in part it is secondary to fever and hyperventilation.

TABLE V

SERUM CALCIUM AND NPN VALUES IN FATAL CASES OF EKIRI

Case No.	Ca mg. %	NPN mg. %
Ke 22	7.9	86
To 42	7.7	64
NIH 4	8.5	64
Toj 45	7.4	55
Ke 21	8.5	90
Ke 29	8.6	90
Ke 36	7.2	74
Toj 50	6.8	62

Fever, hyperventilation, alkalosis, decrease of blood volume, mutually aggravate each other, and lead to increased severity of tetany. These processes effect an increasing anoxia of the body tissues, foremost of the cerebral tissue, with resulting irreversible damage.

The inquiry into the possible causes of the predisposition of Japanese children to tetany led logically to a consideration of the Japanese nutrition. We learned that the Japanese diet is extremely low in calcium, the daily intake of adults being less than 0.3 gm., compared with the American standard of about 1 gm. This lack of calcium is best illustrated by the data on milk consumption, which is about 1.2 cc. of milk per capita per day for the city population. It is only insignificantly higher for the rural population. On the other hand the diet is high in phosphorus, so that the calcium-phosphorus ratio is 1:7, as compared with the generally accepted optimum of 1:1. Japanese infants are breast fed for the most part. They are weaned at about one to two years of age. After weaning their diet qualitatively is in no way different from that of adults. Milk consumption is practically unknown to them. On the basis of their average food intake one may estimate the calcium consumption of children of three to six years of age to range from about 0.1 to 0.15 gm. of calcium per day. In other respects the Japanese diet appears to be fairly satisfactory. The protein intake is about 60 gm./2000 calories; the supply of vitamins, except for vitamin D is reasonably adequate. Rickets is uncommon except in mountain areas, which are lacking in sunshine.

To explore the possibility of the existence of latent tetany, a small scale study of orienting nature was undertaken on a group of 29 Japanese children one to 10 years of

age. Sixteen of them were siblings of patients with Ekiri. Others were well children seen in the clinics. Almost all the children had a positive Chvostek sign, about half of them had some twitching of the muscles or a Trousseau's sign of the hands or feet. One child who had a positive tuberculin test but no evidence of active tuberculous infection was selected for us as a control by his physician because he was a "spastic child." He had

TABLE VI

DISTRIBUTION OF SERUM CALCIUM VALUES IN JAPANESE AND AMERICAN "CONTROL" CHILDREN

Patients	Ca mg. %			Total no. of values
	8 to 9	9 to 10	>10	
Japanese	5	16	10	29
American	0	4	4	8

TABLE VII

DISTRIBUTION OF SERUM INORGANIC PHOSPHORUS VALUES IN JAPANESE AND AMERICAN "CONTROL" CHILDREN

Patients	P mg. %				Total no. of values
	3 to 4	4 to 5	5 to 6	>6	
Japanese	0	7	19	3	29
American	1	5	1	1	8

TABLE VIII

DISTRIBUTION OF SERUM PHOSPHATASE VALUES IN JAPANESE AND AMERICAN "CONTROL" CHILDREN

Patients	Bodansky units Phosphatase							Total no. of values
	4 to 5	5 to 6	6 to 7	7 to 8	8 to 10	10 to 12	>12	
Japanese	1	0	3	6	7	9	3	29
American	5	3	0	0	0	0	0	8

beautiful manifest tetany. The children showed no clinical evidence of rickets except for enlargement of the costochondral junctions. Roentgenograms of long bones of these children and of some of the children with Ekiri and dysentery were not characteristic of rickets, but suggested that there was generalized osteoporosis. Eight American children residing in the Tokyo area were also studied for comparative purposes.

Tables VI to VIII show the results of the chemical studies. It may be seen from Table VI that while none of the American children had a calcium value of less than 9 mg./100 cc. serum, five of the Japanese children had hypocalcemia of such a degree. From Table VII, which contains the data on inorganic phosphorus, the impression is gained that the Japanese children tended to have somewhat high phosphorus values. In Table VIII are listed the data on the alkaline phosphatase activity in the serum. A definite tendency to high values in the Japanese children is evident, with levels exceeding 10 Bodansky units being recorded in 12 instances. Since neither physical nor roentgenologic examinations gave evidence of rickets, the elevations of phosphatase may be interpreted as signifying an increased osteoblastic activity stimulated by the calcium lack in the diet.

These data are compatible with the assumption of a calcium deficiency in the Japanese diet, which, combined with a high phosphorus intake, would lead to the occasional occurrence of latent hypocalcemic tetany, with normal or even high phosphorus values. Factors, producing increased stress on the homeostatic mechanisms, such as infection, heat, diarrhea, convert the tetany into its manifest form.

The peculiar age distribution of Ekiri appears explicable by the changes with age in nutrition and bone growth of Japanese children. Until weaning, with the calcium in the mother's milk counterbalancing the dietary lack of the mineral, the occurrence of frank calcium deficiency would be rare. In the subsequent period of childhood, with rapid bone growth proceeding and with low calcium intake in the diet, calcium deficiency should be frequent in occurrence and severe in degree. Later, with decreasing rate of growth and increasing food intake, the curves of supply and demand would approximate each other again, and the incidence and severity of calcium deficiency would be expected to decrease. The incidence of Ekiri follows in general the predicted course. The disease is rare in the first two years of life, reaches a peak of incidence in the fourth year, to decline subsequently, and to become quite uncommon beyond the tenth year of life.

The fulminant character of Ekiri, the rapid advent of irreversible changes, and frequent delay in initiation of treatment all conspire to lessen the effectiveness of therapy. Logically, prevention would appear to offer much the greater promise. Aside from obvious measures to decrease the incidence of dysentery, an increase of the calcium supply in the diet would rob dysentery in Japan of its specific malignant features. Ideally such an increase in calcium supply would be best accomplished by increasing the intake of milk. Lack of cow herds, of pasture land, the general overpopulation of the Japanese islands make this approach difficult. Instead we have recommended that calcium in the form of calcium carbonate be added to a Japanese staple food, such as rice. A similar measure was adopted by the British government in wartime, when the national bread was enriched by addition of calcium carbonate.

Ekiri, then, represents an example of a disease complex where underlying nutritional and chemical factors determine the course, manifestations, and prognosis of an infectious disease, a relationship which contrasts with the one usually observed where, as for instance in infantile diarrhea, chemical disturbances are secondary to the infectious process. One wonders, to what extent different nutritional conditions may explain the reported variations with locality and time of infections with organisms of relatively constant virulence.

Summary

From a clinical, bacteriologic, chemical and pathologic standpoint, one can conclude that Ekiri is mostly bacillary dysentery complicated by tetany, that the diagnosis of Ekiri may occasionally apply to children suffering from tetany and some other infection or perhaps a noninfectious gastrointestinal upset or even tetany alone.

Manifest tetany as seen in hot summer weather, secondary for the most part to bacillary dysentery infection, is a far more serious disease than rachitic tetany without infection. It is characterized by hyperventilation, lethargy or delirium, tonic spasms of the muscles, vomiting, disturbances of the autonomic nervous system and severe clonic or tonic convulsions. The child may die in a sustained tonic spasm or the tetany may aggravate the fever and dehydration caused by the infection, so that circulatory collapse and cerebral anoxia ensue. Early and strenuous treatment of the tetany, the infection and the accompanying dehydration is necessary if the present high death rate of Ekiri is to be greatly reduced. Prevention of tetany in Japanese children by supplementation of their diet with calcium and of dysentery by improved sanitation would be a far better approach to the problem.

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Spanish Abstract

La Etiologia del Ekiri, Una Enfermedad Altamente Fatal en los Niños Japoneses

En el verano de 1947, un grupo americano que se componía de un Clínico, un Bacteriólogo-patólogo, y un Bioquímico, fueron a Tokio bajo los auspicios del Instituto Japonés de Salubridad y la Sección de Salubridad y Bienestar Públicos de SCAP para estudiar la enfermedad llamada Ekiri. Encontramos que los pacientes con Ekiri tenían signos y síntomas marcados de tetania así como de disentaría. Los síntomas eran hiperventilación, letargía o delirio, espasmos musculares tónicos, desordenes autonómicos del sistema nervioso y convulsiones clónicas o tónicas severas. Se observaron signos y síntomas menos severos de tetania cuando se hizo la diagnosis de disentería bacilar. Los cultivos de los asientos de 106 pacientes rindieron bacilos de disentería en casi cada caso. El exámen después de la muerte reveló inflamación del colón compatible con disentería, en la mayor parte de los casos.

Se caracterizó el desorden químico por cantidades bajas de calcio en el suero, una diminución del contenido CO_2 y tensión de la sangre, y cantidades altas de NPN. Las cantidades bajas de calcio aparecieron compatibles con los signos clínicos de tetania. La tensión CO_2 disminuída y la presencia de valores pH normales demostraron el alto grado de hiperventilación observado clinicamente. Es explicable la elevación de NPN por las grandes pérdidas de agua causadas por la fiebre alta y la hiperventilación, además de las pérdidas de flúido del cuerpo mediante vómitos y diarrea.

A los infantes japoneses se les da, por lo general, el pecho y se despechan al año o a los dos años de edad. La dieta de los niños, similar a la de los adultos, es baja en el consumo de

calcio; los niños de dos a seis años de edad asimilan poco más o menos 0.15 gm. al día. El raquitismo es raro.

Se llevó a cabo un estudio preliminar en 29 niños japoneses de dos a seis años de edad. Se encontraron signos suaves de tetania en una parte considerable de ellos; cinco mostraron cantidades de calcio en el suero más bajas de 9 mg/100 cc. de sangre. Las cantidades de fósforos tendieron a ser más altas que las de los grupos de control americanos. La fosfatasa de suero alcalino era considerablemente elevada, algunas veces en exceso de 10 unidades Bodansky.

Los roentgenogramas no mostraron raquitismo, pero sugerieron una mineralización disminuída. Este informe sostiene la suposición de la deficiencia de calcio en la dieta.

Llegamos a la conclusión de que Ekiri es más bien una disentería bacilar complicada por tetania. Su tratamiento con cloruro de calcio, sulfonamides y grandes cantidades de flúidos parentéricos produjeron algún mejoramiento en el tipo de mortalidad. Si se aumenta la ingestión de calcio en los niños japoneses y se introducen medidas de salubridad pública, se disminuirá la disentería y se evitará grandemente la enfermedad.

Children's Hospital Research Foundation

COMBINED IMMUNIZATION AGAINST DIPHTHERIA, TETANUS AND PERTUSSIS IN NEWBORN INFANTS

I. Production of Antibodies in Early Infancy

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UNTIL the 1920's it was generally accepted that the newborn infant had fully developed the capacity to produce antibacterial and antitoxic antibodies. The admittedly greater resistance to infection of the older child and adult was attributed to an accumulation of benefits from various latent infections.

With the publication of Hirszfeld's[1] work in 1926 the pendulum swung sharply to the other side. He concluded from his investigations that antibodies are to be considered as "biochemical organs," which come to full maturity at different ages in the development of the individual, just as in the case of many other organs and tissues of the body. Hirszfeld did not deny the importance of secondary stimuli in the production of antibodies, but felt their role was entirely secondary until "serological maturity" was achieved.

As far back as 1919 and 1925 German and French investigators[2,3] showed that diphtheria antitoxin response to immunization procedures in young infants was not as satisfactory as in older children. The production of agglutinins against E. typhosa was also noted by German authors[4] to be less in newborns than in adults. Freund[5] in 1930 found that antibody response to injection of various antigens in young animals was not as great as in adult animals. In a series of investigations between 1933 and 1937, Baumgartner,[6,7] working with rabbits, pointed out the effect of age on the production of antibodies. She showed that in these animals there is a curve of development in the ability to produce antisera and that during the course of this immunologic maturation there also is a change in the quality of the antisera elaborated.

The work on this subject has been summarized very completely by Baumgartner[8] and McKhann.[9] It must be concluded that the experimental evidence on hand supports Hirszfeld's concept of a serologic maturation. The production of antibodies in response to an antigenic stimulus on the part of the newborn infant does not correspond qualitatively or quantitatively to that of the fully mature individual.

Recent electrophoretic analysis of maternal and fetal plasma has offered further evidence that there is a difference between the serum proteins of the newborn and those of the adult. Longsworth and collaborators[10] in 1945 showed that fetal sera were poorer than those of adults in total globulin. On the other hand, the relative and absolute concentrations of fetal gamma-globulin were higher than either the normal or maternal values. More recently Moore and co-workers[11] have confirmed these findings and have demonstrated that the gamma-globulins decrease in the first few weeks after birth to

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reach a level which is lower than that of the same fraction in the mother's blood. The subsequent rise of all globulin fractions is very slow and by the age of one year the adult level is not yet reached. Since the gamma component includes many of the antibody globulins these results are consistent with other evidence as to the immunologic processes in newborn infants.

For many years the conclusion that antibody production by newborn infants does not correspond to that of fully mature individuals has been accepted without question. It has been customary, therefore, to start the routine immunizations of children against diphtheria and pertussis during the second half of the first year of life or later. Not starting inoculations against pertussis until six months of age or later leaves infants without protection against this infection for several months or a year. This is the very age period in which the highest mortality occurs. It is worth while recalling that in many parts of this country pertussis causes more deaths in children below one year of age than diphtheria, scarlet fever and measles combined.

The case of diphtheria is somewhat different because the antitoxin passively transmitted from the mother affords, in many instances, protection to the newborn infant. In recent years, however, there has been a decrease and practical disappearance of diphtheria in many areas in the country. As a consequence an increasing number of pregnant women have been found to be Schick positive due to the lack of subclinical stimulation adequate for the production of diphtheria antitoxin. In turn they have been unable to transmit sufficient antitoxin to their offspring to protect them against diphtheria infection.

Active immunization against diphtheria and especially against pertussis as soon as possible after birth is obviously desirable. Efforts have been made by a few investigators to determine whether a significant degree of protection may be obtained by starting the inoculations in early infancy.

The first to describe such experiments in this country was Sako.[12,13] He reported his experience with immunization of several thousand infants against pertussis, some as young as two weeks of age. Sako concluded that young infants are able to produce antibodies just as well as older children, in response to injections of pertussis vaccine. These patients also responded satisfactorily to "stimulating doses" of pertussis vaccine administered eight to 12 months following completion of the initial course. It was his opinion that the reason other investigators had stated that infants have a poor antibody response to pertussis vaccine was their employment of inaccurate laboratory methods for assay of antibodies and the use of fluid vaccine as an immunizing agent. Sako recommended that alum-precipitated vaccine be used in immunization of infants, because it affords prolonged antigenic stimulus and improves antibody production.

Vahlquist[14] recently attempted to immunize a group of children against diphtheria, some of whom were in the newborn period. He used a single injection of alum-precipitated toxoid. In comparing the serum diphtheria antitoxin levels four to five weeks after inoculation he noted that age made no difference in the immune response.

We are thus confronted with two different points of view: that newborn infants are poor producers of antibodies (this might be called the classical conception); and that age influences only to a limited extent the immune response to antigenic stimulation.

The present study was initiated at Babies Hospital in December 1945 in an attempt to find answers to some of these questions.

The results of this investigation will be reported in three sections. This paper deals with antibody levels obtained after prophylactic inoculation of newborn infants against tetanus, diphtheria and pertussis. The second paper will include evidence on the persistence of antibody levels, the antibody response to a booster dose, and the interference of passive immunity with active immunization against diphtheria. The third and final paper will consist of a comparison of immunization results in newborn infants and a group of older children, all injected with the same material and following the same routine. Results of prophylactic inoculation in the latter group, the older children, have been reported previously.[15] Additional observations will be detailed at a later date.

Plan of the Investigation

The present investigation includes 198 normal, full-term infants born in the nurseries of Sloane Hospital. The group was entirely unselected and included 107 male and 91 female infants. Of these, 96 were white and 102 Negro. Only those infants whose homes were in the vicinity of Vanderbilt Clinic were accepted in the experimental group.

TABLE I

Schedule of Inoculation

Age	Injections	Triple combined antigen* (20 billion H. pertussis per cc.)
1 wk.	First	0.5 cc.
5 wk.	Second	1.0 cc.
9 wk.	Third	1.0 cc.
6–12 months	"booster" dose	0.5 cc.

* Cutter's "Alhydrox."

These infants were inoculated against diphtheria, tetanus and pertussis by means of three injections at four week intervals of a triple combined vaccine.*

The results of prophylactic inoculation were evaluated by determination of serum levels of anti-bacterial (agglutinins) and antitoxic antibodies.

Antibody titers were also determined after administration of a booster dose, because it was believed that a more accurate picture of antibody production could thus be obtained.

The schedule of inoculation is detailed in Table I. The first dose of the vaccine was administered while the infants were still in the Sloane Hospital nurseries. The other two injections were given upon return visits to the Pediatric Division of Vanderbilt Clinic. By the age of nine weeks each infant had received a total of 2.5 cc. of the immunizing material containing 50 billion H. pertussis organisms. Most of the booster doses were administered at varying times between six and 12 months of age. For this purpose 0.5 cc. of the same triple combined antigen used in the basic immunization was injected. Further details as to the effects of booster doses on antibody levels will be presented in a subsequent paper.

* Cutter's "Alhydrox."

Blood samples for titration of antibodies were obtained as follows:

1. Before prophylactic inoculation (at one week of age).
2. One month after the last of the three injections (13 weeks of age).
3. Ten to 30 days after booster dose (between six and 12 months of age). In a few cases the interval between the "recall" dose and collection of the blood specimen was longer.

No Schick tests were performed because even the minimal amount of diphtheria toxin involved in this test may result in an increase in antitoxin levels.[16] Therefore, it would be difficult to evaluate the antibody levels attained in response to the experimental vaccine preparation.

Materials Used

The material* used for prophylactic inoculation consists of aluminum hydroxide-adsorbed tetanus and diphtheria toxoids to which are added 20 billion cc. Phase I H. pertussis organisms. The pertussis organisms were grown on human blood and consequently not washed after harvesting. They were killed with merthiolate. The diphtheria toxin used in the preparation of the toxoid had about 30 Lf./cc., the tetanus toxin 100,000 to 120,000 MLD/cc.

Ramon,[17] a number of years ago, was the first to challenge the classical German concept of the "competition of antigens" and showed that an individual could be immunized against several diseases simultaneously. Various authors[18-21] have reported that two or more antigens in combination have a synergic effect. In particular, antibody response to diphtheria and tetanus has been shown to be potentiated by mixtures of the two toxoids. In this country there have been a number of reports in recent years on the use of mixed immunizations.[18-23] The practical advantages in the use of combined vaccines, such as saving of time and decrease in the number of injections, are self evident.

Ramon[17] and Glenny[24] showed as far back as 1925 that it was possible to enhance the immunizing activity of vaccines and toxoids through the effect of nonspecific adjuvants. These substances are for the most part mild irritants, which promote lesions of the tissues and thus permit the antigen to be slowly liberated so as to provide a prolonged and continuous antigenic stimulus.[25] The most widely used adjuvant has been alum; aluminum hydroxide has also been used extensively abroad and more recently in this country.[22, 25]

Laboratory Methods

The levels of diphtheria antitoxin were determined in guinea-pigs by a modification of the Kellogg skin test method,[26] a modification of Roemer's technic.

The tetanus antitoxin determinations were carried out in mice as recommended by the New York State Department of Health.[27]

The serum agglutinins against H. pertussis were titrated by the method described by Flosdorf.[28]

All laboratory determinations were performed by the Biological Control Division of Cutter Laboratories, Berkeley, Calif. All blood samples were labeled according to a code system known to the clinical investigators, but unknown to the group performing the laboratory determinations. The specimens were numbered progressively as obtained and the same code series included not only infants reported in this and the following

* "Alhydrox."

paper, but also children of two series previously reported and those in a third group to be presented at a later date. The coding precautions provided a further check on serum antibody determinations.

Agglutinin and Antitoxin Titers Considered Protective

The results of prophylactic inoculation against diphtheria, tetanus and pertussis were evaluated by determination of the antibacterial (agglutinins) and antitoxic antibodies.

It is fully realized that in the individual case protection or lack of protection against infection is due to many variables of which serum antibody level is only one. Final judgment as to the efficacy of prophylactic inoculation can be made only after clinical exposure to infection. However the correlation between serum antitoxin content and clinical immunity to diphtheria and tetanus is very close. The same is true to a lesser extent of pertussis agglutinins and immunity to whooping cough.

In this study a serum agglutinin titer of 1:400 or higher against H. pertussis has been considered as a satisfactory immune antibody level. This is close to the agglutinin titer of 1:320 that has been shown to afford complete protection against intimate exposure to pertussis.[29,30] It should be kept in mind, however, that while susceptibility does not exist in the presence of agglutinins in high titer, 1:320 or higher, immunity may exist in the absence of demonstrable agglutinins; and a substantial number of subjects with low agglutinin titer are found to be immune when exposed to pertussis.

The conclusions just mentioned were reached by Miller and by Sako after investigations in which they employed a method devised by Miller[31] for titrating pertussis serum agglutinins. The Flosdorf technic which has been followed in the present investigation is said by Miller[32] to give somewhat higher agglutinative titers. However, it should be mentioned that pertussis aglutinin titers (Flosdorf method) observed by us in a previous investigation[15] after immunization with triple combined antigen checked very closely with those obtained by Miller using his own method after immunization with the identical preparation.[22] Only continued observation of individual protection afforded by an agglutinin level of 1:320 or more upon intimate familial exposure to pertussis will reveal whether the difference in results obtained by the two methods is clinically significant. For the purpose of the present investigation a serum agglutinin titer against H. pertussis of 1:400 or higher will be considered "protective."

A level of 0.03 units/cc. or more of diphtheria antitoxin was considered as affording complete protection to the individual. Titrations were not carried out below this level. It should be noted that the minimum level tested for is in reality seven and a half times as great as the 0.004 units/cc. generally accepted as sufficient to induce Schick negativity in the majority of individuals.[33]

The amount of antitoxin in the blood necessary to protect against tetanus has not been definitely established. Attempts have been made to estimate the protective level of antitoxin by analogy with titers following passive immunization. A titer of 0.1 unit/cc. has been generally considered as affording protection against infection by Clostridium tetani.[16,34] However, Cooke and Jones[35] emphasized that there is evidence that higher antitoxin values are necessary to protect passively immunized animals than those immunized actively. The minimum level of tetanus antitoxin tested for was 0.01 unit/cc. Tetanus antitoxin units in the present investigation refer to American units. It should be remembered that units of diphtheria and tetanus antitoxin are not directly comparable.

While a unit of tetanus antitoxin protects a guinea-pig of 350 gm. body weight against 1000 MLD of tetanus toxin, one unit of diphtheria antitoxin protects a guinea-pig of 250 gm. against only 100 MLD of diphtheria toxin.

The use of the term "protective titer" has been questioned and the phrase "protective range of titers" suggested. The difference is one of terminology. For the sake of brevity

TABLE II

REACTIONS TO INOCULATION

Age	Injection	Total no. of injections	Local reactions							
			Erythema (cm.)				Infiltration (cm.)			
			0 (%)	<2.5 (%)	2.5–5 (%)	>5 (%)	0 (%)	<2.5 (%)	2.5–5 (%)	>5 (%)
1 wk.	First (0.5 cc.)	150	68	22	9	1	61	37	2	0
5 wk.	Second (1.0 cc.)	139	72	21	5	2	70	25	5	0
9 wk.	Third (1.0 cc.)	114	61	19	18	2	60	30	10	0

Age	Injection	Total no. of injections	Systemic reactions					
			Fever (%)			Other reactions (%)		
			None	Slight (37.8°-38.9°)	High (38.9°–40.0°)	Irritability	Vomiting	Anorexia
1 wk.	First (0.5 cc.)	150	100	0	0	0	0	0
5 wk.	Second (1.0 cc.)	139	80	19	1	33	1	4
9 wk.	Third (1.0 cc.)	114	80	11	9	40	1	7

and clarity in reporting results, the term "protective titer" will be used with full realization of its shortcomings.

LOCAL AND SYSTEMIC REACTIONS TO INOCULATION

The injections of triple combined antigen were given in the buttocks to about half the patients and to the other half in the deltoid region. No difference was observed in the two groups, in the occurrence of local or systemic reactions.

In all cases, the vaccine was injected deep subcutaneously or intramuscularly. Special

attention was given to avoiding introduction of the immunizing material into the skin when the needle passed through it, as suggested by Sako.[12] No effort was made to point the needle downward, as recommended by Sauer.[36]

The local and systemic reactions to 403 injections are detailed in Table II.

Between 60% and 70% of all patients had no local reactions to injection of the vaccine. In almost all others, reactions at the site of injection were of moderate intensity. Erythema and induration, when present, became apparent within 12 to 24 hours and lasted an average of 48 hours. In almost all infants a small, nonpainful, deeply seated nodule was present at the site of inoculation for several weeks. No significant difference

TABLE III

TITRATION OF SERUM AGGLUTININS AGAINST H. PERTUSSIS

Agglutinin titers	Number of cases		
	Before inoculation (1 wk. of age)	One month after third injection (13 wk. of age)	10–30 days after booster dose (6–12 mo. of age)
1:0	141 (98%)	38 (30%)	15 (16%)
1:50	—	5	2
1:100	—	3	5
Breakdown of titers 1:200	2	11	23
1:400	—	16	12
1:800	—	19	14
1:1600	—	12	20
1:3200	1	21 (17%)	10 (11%)
Without protective titer*	143 (99.5%)	57 (45.6%)	35 (38.5%)
With protective titer	1	68 (54.4%)	56 (61.5%)
Total cases	144	125	91

* "Protective" agglutinin titer—1:400 or higher.

was observed in the number or the intensity of local reactions to the first, second or third injection of the immunizing agent.

Five sterile abscesses were observed from the more than 500 injections given, an incidence of approximately 1%. In three cases, the inoculations resulting in sterile abscess had been given in the buttocks, in the other two in the deltoid region. Four of the five infants had subsequent injections of the triple combined vaccine without untoward reactions. The fifth child did not return for further injections.

In contrast to the local reactions the incidence and severity of systemic reactions increased with subsequent injections. As can be seen from Table II, no systemic manifestations, in particular no fever were observed immediately following the first injection of triple combined antigen given, as it will be recalled, at the age of one week.

The situation changed considerably after the second injection and even more after third injection. At the age of nine weeks, 11% of the patients showed a moderate elevation of temperature, and 9% had fever of more than 38.9°C. Forty percent of the total were irritable for varying periods of time.

Febrile reactions usually appeared 12 to 24 hours after injection and in almost all cases the temperature returned to normal within 24. hours.

The lack of reactivity to infectious and other stimuli characteristic of infants in the newborn period explains the absence of systemic reactions. Lack of fever in the presence of infection, even severe infection, is commonly found in this age group. As infants grow older, febrile and other systemic responses to infectious stimuli increase as is clearly indicated by our figures. Regarding local reactions, it is interesting to note that the same pattern is not followed. Local reactivity, at least to inoculation of antigenic

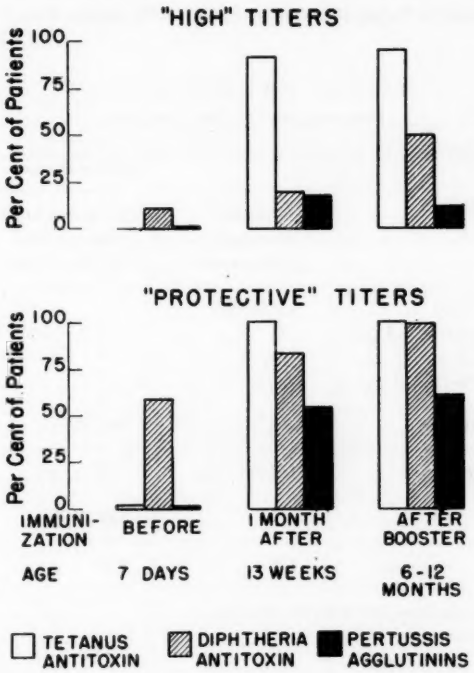

FIG. 1. Titration of Antibodies Before and After Immunization with Triple Combined Antigen. In this figure the word "immunization" is used to signify the administration of a complete series of prophylactic injections as described in the text.

material, seems to be as great at birth as after several weeks of life. No neurologic complications were noted in this group of cases.

As stated elsewhere[15] analysis of the data reveals that reactions in the individual are usually unpredictable. On the basis of previous experience it is impossible to predict response by the same child to subsequent injections of vaccine.

TITRATION OF SERUM AGGLUTININS AGAINST H. PERTUSSIS

The results of titration of serum agglutinins against H. pertussis are detailed in Table III and represented graphically in Figure I.

Agglutinin titers for H. pertussis were determined in 144 newborn infants at seven days of age, prior to inoculation. In 141 cases (98% of the total), serum agglutinins against H. pertussis could not be demonstrated. The fact that pertussis agglutinins are not usually present in the serum before active immunization is in agreement with the findings of most investigators.

One month after completion of the series of injections, at 13 weeks of age, 125 infants were tested. Of these, 68 (54.4%) had a pertussis agglutinin titer of 1:400 or higher, a level believed to afford complete protection. The difference in agglutinative titers before and after inoculation is obviously very significant. It should also be noted in the breakdown of titers detailed in Table III, that 21 cases (17% of the total) had a "high titer"

TABLE IV

TITRATION OF TETANUS ANTITOXIN

Antitoxin titers (units/cc.)**	Number of cases		
	Before inoculation (1 wk. of age)	One month after third injection (13 wk. of age)	10–30 days after booster dose (6–12 mo. of age)
Breakdown of titers			
<0.01	131 (85%)	—	—
>0.01<0.1	21	—	—
0.1	—	—	—
>0.1<1.0	4	7	2
1.0	—	3	2
>0.1	—	118 (92%)	90 (96%)
Without protective titer*	152 (98.5%)	0	0
With protective titer	4	128 (100%)	94 (100%)
Total cases	156	128	94

* "Protective" antitoxin titer—0.1 unit/cc. or more.
** Units refer to American units.

of agglutinins (1:3200 or higher), while in 38 (30%) no agglutinins could be demonstrated.

Ninety-one cases were tested 10 to 30 days after a booster dose which was given between the ages of six and 12 months. Inspection of Table III shows that there was only slight change in the percentage of patients with a "protective" titer before and after the booster dose. If the total number of cases with an agglutinin level of 1:1600 or more is taken into account it will be seen that their percentage did not increase significantly after the booster dose.

A difference, however, exists in the number of patients in whom pertussis agglutinins could not be demonstrated before (30% of the total) and after booster dose (16%). This difference is of borderline statistical significance ($X^2 = 4.78$; $P = 0.02$) and is probably not due to chance alone.

It has been stated by Sauer[37] that "the earliest age at which most infants develop

pertussis antibodies from three doses of plain vaccine is the sixth or seventh month of life." Adams and collaborators [38] state that their results in part confirm this observation. It is apparent from our results that the great majority of infants in whom the inoculations are completed by the age of nine weeks will have developed antibacterial antibodies (agglutinins) by the age of three months. It is also interesting to note the difference in the percentage of patients showing no agglutinins in the serum before and after the booster dose. This points clearly to the fact that in many instances patients whose antibody-forming tissues are sensitized to the antigen but who fail to produce circulating antibodies, may do so upon subsequent contact with the antigen (booster dose). Titration of antibodies after a booster dose thus gives a more accurate picture of antibody production than is otherwise obtained.

Titration of Tetanus Antitoxin

Titrations of the serum levels of tetanus antitoxin are recorded in Table IV.

One hundred and fifty-six infants were tested prior to injection of the vaccine at one

TABLE V

Titration of Diphtheria Antitoxin

Antitoxin titers (units/cc.)	Number of cases		
	Before inoculation (1 wk. of age)	One month after third injection (13 wk. of age)	10–30 days after booster dose (6–12 mo. of age)
<0.03	70 (42%)	19 (15%)	1
0.03	3	3	1
Breakdown of titers >0.03<0.1	15	10	3
0.1	8	4	6
>0.1<1.0	40	47	30
1.0	11	15	5
>1.0	21 (12%)	25 (20%)	45 (50%)
Without protective titer*	70 (41.6%)	19 (15.4%)	1
With protective titer	98 (58.4%)	104 (84.6%)	90 (99%)
Total cases	168	123	91

* "Protective" antitoxin titer—0.03 unit/cc. or more.

week of age. Of the total tested at this time, 85% had less than 0.01 units/cc. of antitoxin, the minimum level tested for. Except for the isolated statement of Ten Broeck and Bauer[39] that tetanus antibody was present in the serum of persons in China who carried tetanus bacilli in their intestine, tetanus antitoxin has heretofore been reported as normally not occurring in the blood of humans. This is the first time (to the author's knowledge) that appreciable levels of tetanus antitoxin in the circulation have been found before immunization. This finding can be explained by the fact that for several years in New York City most children and adolescents going to summer camp have been immunized against tetanus. It can be expected therefore that a substantial number of

young mothers have circulating tetanus antitoxin which they can transmit through the placenta to their offspring.

One month after completion of the inoculations all of the 128 patients tested had a tetanus antitoxin titer of 0.1 units/cc. or more (a level generally considered as affording protection). Of the total tested 92% had a "high" level of more than 1.0 unit/cc. of serum.

After a booster dose, the results were not significantly different. It must be recognized however that, since 1.0 unit/cc. was the maximum level tested for, it was not possible to detect any increase in antitoxin titers beyond this level that may have taken place after booster.

The levels of tetanus antitoxin obtained after immunization were unusually high. This demonstrates that young infants have fully developed the capacity to produce tetanus antibodies in response to a strong antigenic stimulus. It has already been noted by others[34] that triple combined antigen* used contains tetanus toxoid of high antigenic value.

Figure 1 clearly indicates the high levels of tetanus antitoxin achieved after a full series of immunizing injections.

Titration of Diphtheria Antitoxin

Results of the titration of diphtheria antitoxin in the serum of infants before and after inoculation are tabulated in Table V and Figure 1.

A new element is introduced here in that of the 168 patients tested before injection, 58.4% had a diphtheria antitoxin level of 0.03 units/cc. or more. This antitoxin was obviously passively transmitted from the mother to the child through the placenta before birth. If we recall that the minimum antitoxin level tested for is greater than the amount needed in the majority of instances to induce Schick-negativity, it follows that more than 60% of the mothers in the present series must have been Schick-negative. This figure checks fairly closely with some of the surveys made in this country, but is higher than others.[40] Environmental factors and the economic status of the groups under investigation presumably explain these discrepancies.

One month after completion of the immunizing series 84.6% of the 123 patients tested had an antitoxin level of 0.03 units/cc. or more of serum (titers within the protective range), and 20% had a "high" titer of more than 1.0 units/cc. The difference in the numbers of infants with a "protective" titer before and one month after immunization is highly significant statistically and could not be due to chance alone ($X^2 = 21.7$; $P = « 0.0001$). There is an increase in the number of patients with an antitoxin titer of more than 1.0 unit/cc. from 12% to 20%, although it is not within the limits of significance ($X^2 = 2.67$; $P = 0.10$).

After a booster dose the percentage of "protected" children rose very significantly from 84% to 99% ($X^2 = 11.07$; $P = 0.0009$). At the same time there was a very marked rise in the percentage of patients with titers of more than 1.0 units/cc. from 20% to 50% ($X^2 = 18.8$; $P = < 0.0001$).

The increase in the number of cases with a "protective" titer before and after prophylactic inoculation, which, as has been said, cannot be due to chance distribution, points to the fact that active immunization was achieved in almost all instances despite

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* "Allhydrox."

the passively transmitted diphtheria antitoxin present in over half the cases. This is further emphasized by the results of titrations after the booster dose, which also stress the role of "recall" injections in bringing forth tissue response to prophylactic inoculation.

Evidence will be presented in a subsequent paper regarding interference of passively transmitted antitoxin with active immunization against diphtheria.

Summary

This investigation was undertaken to determine the capacity of newborn infants to produce antibodies. One hundred and ninety-eight infants were inoculated against diphtheria, tetanus and pertussis. A triple combined antigen containing aluminum hyroxide-adsorbed tetanus and diphtheria toxoids and 20 billion/cc. H. pertussis organisms was used. First injection (0.5 cc.) was given at seven days, second (1.0 cc.) at five weeks and third (1.0 cc.) at nine weeks of age. A booster dose of the same triple combined antigen (0.5 cc.) was given between six and 12 months of age.

Local and systemic reactions to 403 injections showed an increase in the number and severity of systemic reactions with subsequent injections; no such difference was observed in local reactions. Five sterile abscesses were noted in more than 500 injections, an incidence of about 1%. No neurologic complications were observed.

More than half the newborn infants tested showed diphtheria antitoxin levels of 0.03 units/cc. or more before inoculation. In 98% of those tested at one week of age, agglutinins against H. pertussis could not be demonstrated. Fifteen percent of newborns studied had detectable levels of tetanus antitoxin before prophylactic inoculation.

One month after a third injection all infants tested had tetanus antitoxin levels of 0.1 unit/cc. or more ("protective level"), 92% reaching "high" antitoxin levels of more than 1.0 unit/cc.

At this same age, 13 weeks, 84% had diphtheria antitoxin levels of 0.03 units/cc. or more ("protective level"). After booster dose this percentage increases from 84% to 99%.

One month after completion of inoculations about 60% of the children had pertussis agglutinin levels considered "protective" (1:400). A booster dose failed to elicit any change in the number of patients with these high agglutinin titers. However, the booster caused a decrease in the percentage of infants showing an absence of pertussis agglutinins in the serum after the three initial injections.

It is concluded that newborn infants do produce antibodies in response to antigenic stimuli. Response to booster dose was further evidence of the immune status of most of these patients.

Further evaluation of the data and a comparison of antibody production in newborn infants with that of older children will be undertaken in a subsequent paper.

Acknowledgements

We wish to acknowledge our indebtedness to Dr. Walter E. Ward, Medical Director of Cutter Laboratories, whose cooperation and assistance made this investigation possible. Our sincere appreciation is also extended to Mr. R. B. Clark, former Director, and Dr. E. H. Newkom, present Director of Clinical Research, for their helpfulness and support.

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SPANISH ABSTRACT

Immunizacion Combinada Contra Difteria, Tetanos y Pertussis en los Infantes Recien Nacidos. I. Produccion de Anticuerpos en Infantes Recien Nacidos

Para determinar la capacidad de los infantes recien nacidos para producir anticuerpos, se inocularon 198 infantes contra difteria, tétanos y pertusis. Se usó una vacuna combinada triple conteniendo tétanos adsorbido en hidróxido de aluminio y toxoides de difteria y 20 billones/cc. de organismos de H. pertussis. La primera inyección (0.5 cc.) fué puesta a los siete días, la segunda (1.0 cc.) a las cinco semanas y la tercera (1.0 cc) a las nueve semanas de edad. Se les dió una dosis fomentadora de la vacuna combinada triple (0.5 cc.) entre los seis y doce meses.

Las reacciones locales y sistemáticas a los 403 inyecciones mostraron un aumento en el número y severidad de las reacciones sistemáticas con inyecciones subsecuentes, y no hubo tal diferencia en las reacciones locales. Se notaron cinco abcesos estériles en más de 500 inyecciones, una incidencia de poco más o menos 1%. No se observaron complicaciones neurológicas.

Más de la mitad de los infantes recien nacidos que pasaron este ensayo mostraron cantidades antitoxinas de difteria de 0.03 unidades/cc. o más antes de la inoculación. En el 98% de estos ensayos a la semana de edad, no se pudieron demostrar las aglutinas contra pertussis H. Quince por ciento re los recien nacidos estudiados tenían cantidades apercibibles de antitoxina de tétanos antes de la inoculación profiláctica.

Un mes después de una tercera inyección todos los niños bajo ensayo tenían cantidades de antitoxina tétanos de 0.1 unidades/cc. o más (cantidad protectora), 92% alcanzaron niveles altos de antitoxina de más de 1.0 unidades/cc.

A esta misma edad, 13 semanas, 85% tenían niveles de antitoxina difteria de 0.03 unidades/cc. o más (cantidad protectora). Después de una dósis fomentadora este porcentaje aumentó de 84% a 99%.

Un mes después de la terminación de las inoculaciones cerca del 60% de los niños tuvieron cantidades aglutinas de pertussis consideradas "protectoras" (1:400). Una dósis fomentadora dejó de traer un cambio en el número de pacientes con estos altos títulos aglutinos. Sin embargo, la inyección de fomento causó una diminución en el porcentaje de infantes mostrando una aunsencia de aglutinas pertussis en el suero después de tres inyecciones iniciales.

Se puede llegar a la conclusión de que los infantes recien nacidos producen anticuerpos en respuesta a los estímulos antigénicos. La respuesta a la inyección de fomento se vió además en el estado inmune de la mayor parte de estos pacientes.

3975 Broadway

ADJUSTMENT OF ELECTROLYTES AND WATER FOLLOWING PREMATURE BIRTH
(With Special Reference to Edema)

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PREMATURE infants at the Boston Lying-in and Children's Hospitals are given no food or water for two to three days after birth. This regimen was introduced by Dr. Stewart Clifford,[1] not only to avoid the danger of aspiration but also because clinical observation of these patients had revealed the frequency of generalized edema, often associated with other disturbances and usually disappearing within the first few days. This routine has permitted the study of alterations in the balances of electrolytes, nitrogen, and water not only while all intake was withheld during fairly prolonged periods, but for varying times thereafter.

METHODS

The present report is based upon complete collections of urine obtained throughout the period of routine thirsting and fasting, and continued for two days or more after feeding was begun. The collections were made from 12 male premature infants, by means of funnel-shaped glass tubes fastened over the penis and delivering the urine by gravity through rubber tubing into a flask in the incubator or below the bassinet. The voidings were not separately analyzed but were allowed to accumulate under a few cubic centimeters of thymol-toluene preservative over periods usually of 24 hours, or until the regimen was changed.

Analyses were performed as follows: Blood urea in 0.2 ml. whole blood by urease method;[2] blood sodium in 0.2 ml. serum measured with the flame-photometer by Wallace's technic.[3] Urine urea in 2 ml. sample by urease method,[2] sodium and potassium in 1 ml. by flame-photometer,[3] chloride in 2 ml. sample by Volhard titration after open Carius digestion,[4] total nitrogen in 0.01 ml. by a modification of the NPN method,[5] and total-solids by calculation from depression of the freezing point.[6]

CLINICAL DATA

Table I presents certain basic data concerning the infants during the period before food was given. Infants 1 to 10 were given no fluid of any sort until from 52.5 to 112 hours after birth. The delay of 112 hours in Infant 8 was not for experimental reasons but because of respiratory difficulty and persistence of edema. Water was administered

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Dr. Yudkin and Dr. Young participated in this study as Nuffield Fellows in Child Health from London and Birmingham respectively; Dr. Minkowski as Rockefeller Fellow in Pediatrics from Paris.

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by gavage to Infants 11 and 12 at 4-hour intervals from 16 until 72 hours after birth. The first administration of food to all 12 infants consisted of from 4 to 8 ml. of 10% glucose solution. This was continued in increasing amounts at 3 or 4-hour intervals, and replaced within or following the next 24 hours by human milk or modified cow's milk formulae.

Only very brief remarks as to the obstetric histories are given in Table I, since detailed study of the mothers' records has disclosed no definite relationship between maternal or birth history and any feature of the data to be presented. The birth weights ranged from 1530 to 2265 gm. All of the infants were cared for in the similarly air-conditioned premature nurseries of either the Boston Lying-in or the Children's Hospital. All were

TABLE I

Infant	Obstetric history	Birth weight (gm.)	Respiration		Edema	Thirsting & fasting (Hr.)	Highest temp. (C.)	Weight loss (%)	Urine volume (ml./sq.m./hr.)	Maximal urine concentration (mosm./l.)
			Onset	Later difficulty						
1. Ha	Normal delivery	2103	Prompt	None	0	54	36.7°	4.1	5.9	400
2. K	Normal delivery	1648	Prompt	None	0	57	36.9°	7.2	8.6	618
3. H	Late fetal distress; normal delivery	1530	Slightly slow	None	?	52.5	38.3°	8.2	6.9	536
4. L	Normal delivery	1625	Prompt	None	?	75.5	36.5°	12.3	6.2	570
5. C	Breech	1956	Prompt	None	+	60	36.7°	10.0	7.4	468
6. S	Slight fetal distress; breech	2265	Slow	None	++	72	36.7°	13.0	11.4	510
7. Hi	Possible toxemia; cesarean	1685	Prompt	Slight	++	69	36.5°	17.5	12.5	478
8. Do	Normal delivery	2210	Prompt	Difficult for 3 days	++	112	36.2°	20.0	6.3	578
9. J	Possible toxemia; repeat cesarean	2260	Prompt	Grunting for 3 days	+++	74.5	36.1°	15.5	17.5	527
10. G	Normal delivery	1655	Prompt	Grunting for 1 day	+++	69	36.5°	19.0	12.6	624
						Fasting (Hr.)				
11. D	Twin, breech	2238	Prompt	None	0	72	36.9°	7.5	22.4	218
12. I	Low forceps	1970	Prompt	None	++	72	37.2°	5.8	22.8	338

and have remained in satisfactory clinical condition except for certain indications of respiratory distress in some during the first few days of life (see Table I); in only one infant did elevation of temperature above 36.8°C. occur. Post-natal weight losses ranged from 4.1% to 20% of birth weight.

The one clinical feature most definitely distinguishing one infant from another was edema, some degree of which was observed at birth in seven of the total group of 12 infants. In two others its presence was questionable, and in only three was it clinically absent. This frequency, which is fairly representative of that generally noted in these nurseries, suggests that edema is more common at and after premature birth than is sometimes appreciated. It seems significant that persistent respiratory distress after birth occurred only in the edematous infants, but we have no means of knowing whether this indicates that the edema involves the lungs as well as other parts of the body.

Results

Serum proteins: Measurements of serum protein made in specimens from several premature infants before this study was begun, and from the first few of those presented

here, revealed considerable overlapping of individual values and no definite correlation with the presence or absence of edema. From these data and those of other workers[7,8] we believe that the edema of premature infants cannot be explained by the level of serum proteins.

Urine volumes: From Table I, it will be noted that the volumes of urine produced

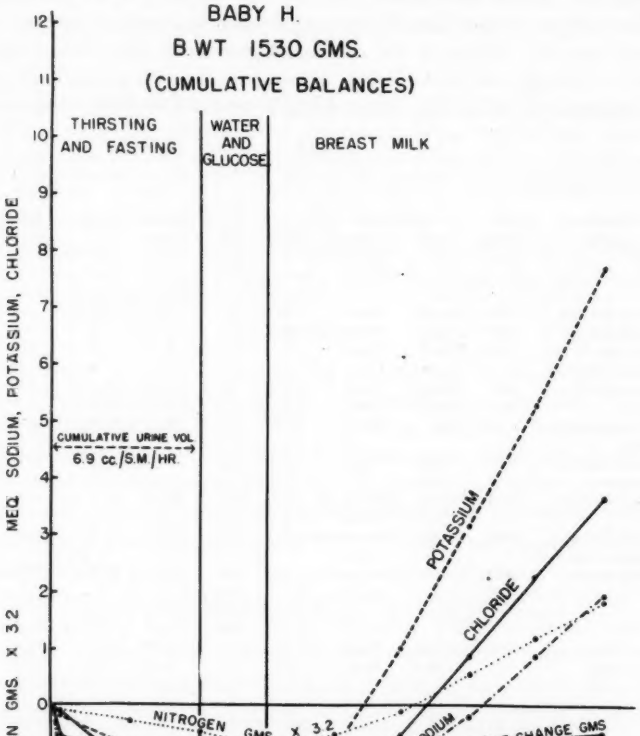

CHART I. Cumulative balances and weight change, Infant 3, during eight days after birth. Not clinically edematous.

during the period without intake of fluids varied over the strikingly wide range of 5.9 to 17.5 ml./sq.m. body surface per hour. Even the relatively small outputs of the non-edematous babies were greater than those of a few full term infants studied under similar circumstances at the Boston Lying-in Hospital. Moreover, recalculation of data published by Thomson[9] indicates that full term infants receiving about 100 ml. of milk

during the first 48 hours have urine volumes of about 4 ml./sq.m./hr. It would appear, then, that the premature infant, with no fluid intake at all, either has available or makes available more water for urine formation than does the full term infant given the breast during the first two days of life.

Concentration of total solids: The first urines voided after birth were dilute,[10] but during the period without water intake the osmolarity, or concentration of total solids in the urine, rose to the maximum listed for each infant in Table I. These values may be somewhat below those attained just before water was provided since the specimens were collected in 24-hour pools. The maximal concentrations were similar in the edematous and nonedematous babies. In preliminary studies[11] of a larger series of premature infants and a few full term newborn infants similarly denied water, it was found that in both groups the maximum concentration of a single voiding rarely exceeded 650 mosm./l. Since the maximal osmolarity of the urine of newborn premature infants equalled that of infants born at term, the relatively larger urine volumes after premature birth cannot be explained by increased water loss due to limitation in concentrating power of the kidney. However, the maximum urine osmolarity of all the newborn infants we have studied has been much lower than the figure of 1400 achieved by infants of two to three months studied by Pratt, Bienvenu, and Whyte[12] on intakes of undiluted evaporated milk. Although the amounts of solids requiring excretion must have been somewhat different, since the newborn babies investigated by us were not given food, it is probable that all infants are limited in their capacity to conserve water in early postnatal life by the limited concentrating power of the kidneys.

Electrolyte and Nitrogen Balances: Thus far, discussion has been confined to certain broader aspects of the period preceding administration of fluids and food. The excretion of individual elements during this period can best be considered by charts of balance studies extended to include the phase of early feeding as well. Since the results seemed to suggest that the balances followed one of two general patterns, a characteristic example of each will be presented. The first (Chart I) is from Infant 3, who was only questionably edematous, and whose urine volume during 52.5 hours without water was 6.9 ml./sq.m./hr.

It will be noted from Chart I, which is constructed from cumulative balances, that during the phase of thirsting and fasting, Na, Cl, K, and N were lost from the body. Since the ordinate scale for N has been adjusted to the normal K:N ratio in cell fluid (3.2 mEq. K: 1 gm. N), we can see that this phase was marked by a relatively larger loss of K than of N. A similar phenomenon occurs in other conditions of dehydration[13] and is certainly not peculiar to the newborn premature infant.

There was little notable change during the glucose period, but as soon as electrolytes and nitrogen were provided by the breast milk, there was a retention of Na, Cl, K, and N. As the slope of the lines indicates, excess retention of K relative to N began at once, and continued not only until the N balance regained the base line but throughout the five days of feeding during which data were obtained. It is interesting to see that Cl retention exceeded that of Na for it might have been expected that Na and Cl would be retained more or less in their normal extracellular ratio (140 mEq. Na:100 mEq. Cl). This suggests that Na which must have been required to preserve the ratio was made available from Na coming from within the cells. Here it should be admitted that the amounts of Na and Cl apparently retained were certainly overestimated since no

correction is available for the loss of these electrolytes through the skin. This, however, would not affect the general relationship.

Chart II, which is constructed on exactly the same plan, exemplifies the second pattern. It shows the cumulative balances from Infant 10 of Table I, who was markedly

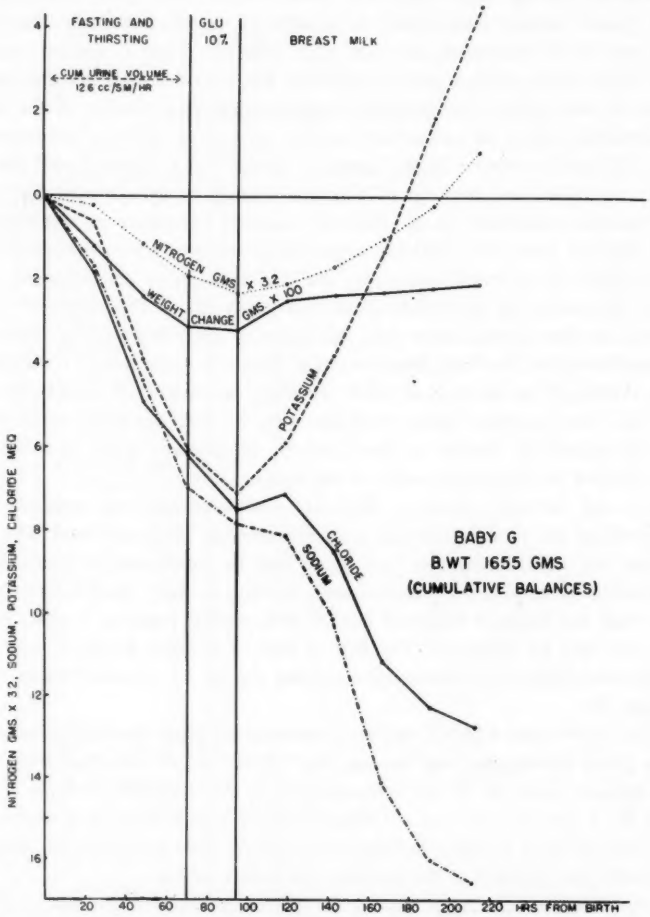

CHART II. Cumulative balances and weight change, Infant 10, during nine days after birth. Clinically edematous.

edematous at birth and whose urine output was 12.6 ml./sqm./hr., or roughly twice that of the infant just presented. During fasting and thirsting the cumulative losses are similar in kind but not in degree to those shown in the preceding chart, for almost three times as much Na, Cl, K, and N were lost by this edematous baby. Following the provision of food, the intracellular elements, K and N, were again retained; on the other hand, the infant continued to discard amounts of Na and Cl equivalent to almost 100 ml. of

normal saline, or 130 ml. of extracellular fluid. There was simultaneous disappearance of clinical edema. The relatively excessive retention of K compared with N was as notable as in the nonedematous infant.

To save space, similar charts for the other infants are not reproduced here, but Table II lists their losses during the period of thirsting and fasting. Variations in routines

TABLE II

TOTAL OUTPUT (sq.m./hr.) DURING THIRSTING AND FASTING

Infant	Edema	Urine (ml.)	Total solids (mEq.)	Sodium (mEq.)	Potassium (mEq.)	Chloride (mEq.)	Nitrogen (mg.)
1. Ha	0	5.9	1.56	0.180	0.140	0.204	18.2
2. K	0	8.6	2.4	0.326	0.248	0.280	15.0
3. H	?0	6.9	2.0	0.270	0.220	0.260	23.9
4. L	?0	6.2	2.1	0.115	0.210	0.083	33.0
5. C	+	7.4	3.14	0.236	0.450	0.133	42.5
6. S	++	11.4	2.5	0.280	0.310	—	35.7
7. Hi	++	12.5	5.5	0.850	0.690	—	74.8
8. Do	++	6.3	3.35	0.170	0.390	—	49.4
9. J	+++	17.5	3.45	0.880	0.700	—	76.6
10. G	+++	12.6	5.5	0.720	0.640	0.726	61.0
			(During fasting with ample water intake)				
11. D	0	22.4	4.0	0.64	0.37	0.66	30.1
12. I	++	20.8	4.6	0.25	0.39	0.333	66.1

TABLE III

SERUM SODIUM (MEQ./L.)

Infant	Day of life 1	2	3	4	5	6	7	8	9
1. Ha			168						
2. K	152		159			148			
3. H	141.5		155					140	
4. L	150			152.5					
5. C	150		152		150				
6. S	142		152		149				
7. Hi	150		172		150				
8. Do	144				170	151			
9. J	140			156.5	150.4				
10. G	150		170						155
11. D	134		138.8						
12. I	150		145						

(|—Vertical line represents time of first fluid intake.)

of feeding, duration of collections, and rates of retention have rendered impossible a convenient arrangement of the numerical data covering the succeeding period of feeding. As the table indicates, the other three infants (1, 2, and 4) with little or no edema showed the same relatively small outputs of urine, Na, Cl, K, and N as did Infant 3 (Chart I). Likewise, although the further data are not tabulated, these nonedematous infants subsequently retained all of the substances mentioned, notably K. On the other hand, and with the admitted exception of infants 5 and 8, those with edema followed

the general pattern of Chart II in that they lost more of all substances during the first phase. Furthermore, while retaining K and N following feeding, they continued to lose Na and Cl as their clinical edema continued to decrease. As Table III indicates, serum Na concentrations rose in all infants during the period without intake, which would suggest that the limited concentrating powers of the kidney had necessitated excretion of water which might otherwise have been conserved.

The metabolism of N deserves special comment. As mentioned above, and as shown by the figures of Table II, losses of N were greater among the edematous babies. Moreover, the N retention of these infants was comparatively low following feeding. This

TABLE IV

BLOOD UREA (mg./100 ml.)

Day of life:		Birth (Cord blood)	1	2	3	4	5	6	7	8
♯(Normal full term Infants)		18.9* (8 to 28.8)**		29.1* (18.5 to 39.6)**			19.7* (9.9 to 27.4)**		16.8* (10.4 to 25.0)**	
Infant	Edema									
1. Ha	0				24.0					
2. K	0	18.8	20.1	19.0	19.8	19.8	28.1	26.0		
3. H	?	15.0	23.0	22.0	24.0	22.0	23.0			
4. L	?	16.1		42.5		50.1	47.8	41.6	29.4	
5. C	+		42.0		56.6	37.0	39.0			
6. S	++	11.3	31.7	30.4	29.9	28.2	20.0			
7. Hi	++		53.0		51.0		37.0			
8. Do	++		31.0	43.0	43.0		74.0	84.0		
9. J	+++	14.0		61.0	51.0	42.0	30.0	25.0		
10. G	+++	12.1	53.2	67.0	65.1	55.7	46.1	28.3		
12. I	++		23.8	58.3	40.2	28.7	18.5	15.9	20.3	20.8

♯ Data of McCance and Widdowson (13).
* Average.
** Range.
Vertical Line (|) indicates beginning of fluid intake.

excessive outgo and slow reaccumulation of N must presumably be a consequence of increased breakdown of body protein beginning immediately after birth. It is interesting in this respect to compare the blood ureas of these infants with those of the non-edematous ones. The figures are given in Table IV. Although the data for non-edematous prematures are quite similar to those of full term infants,[14] the blood ureas of all edematous babies are distinctly higher from within a few hours after birth. Since calculations have shown comparable clearances of urea in all the infants studied and since the urine volumes were larger in the edematous ones, urea must have been produced at a higher rate by these infants. Thus, although we can merely report the observation but cannot explain its significance, there appears to be some relationship between edema at premature birth and increased protein catabolism.

It is of interest to note from Table IV that Infant 8 showed the large N loss and high blood urea consistent with his clinical edema, whereas a small loss of Na (and retention after feeding) makes him a striking exception to the usual course of the edematous babies. This inconsistency, also suggested by Infant 5, was outstandingly displayed by one of the two babies given water early. Discussion of its significance will be postponed until that infant (12) is considered below.

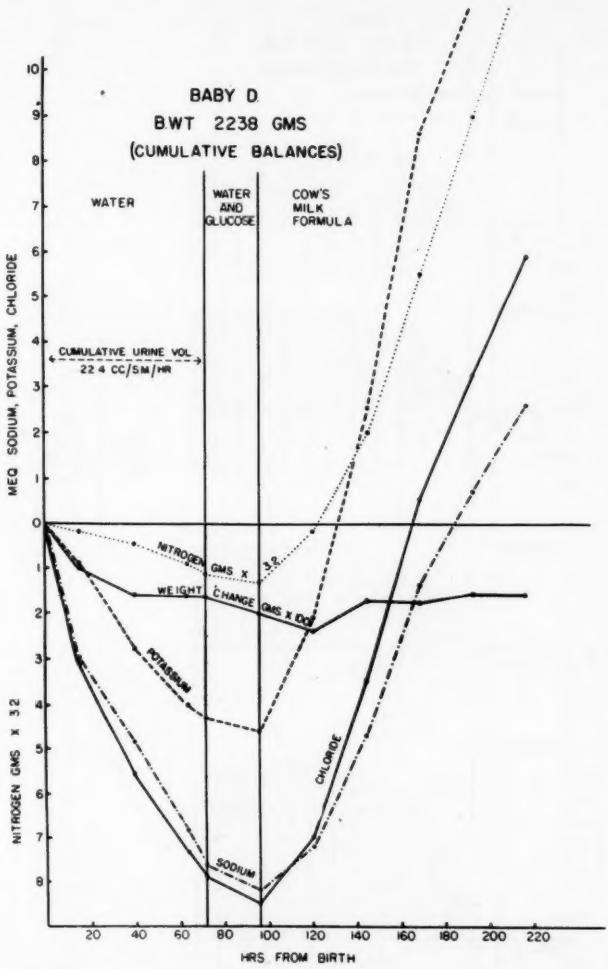

CHART III. Cumulative balances and weight change, Infant 11, during 10 days after birth. The infant, not clinically edematous, was given water freely from 16 hours. Balance data are presented as daily amounts in Chart IV.

Effect of early administration of water: Since it was felt that many of the results obtained might have been different if the kidney had been provided with ample water, Infants 11 and 12 were given water by gavage from 16 hours after birth. In addition, the balance studies of these two babies were continued for much longer periods because of curiosity as to the ultimate adjustment of the early and excessive retention of K already described. Since Infant 11 was not edematous and Infant 12 was moderately so, discussion of their results must be presented individually.

Chart III shows the cumulative balances of Infant 11 for the first 10 of the 16 days

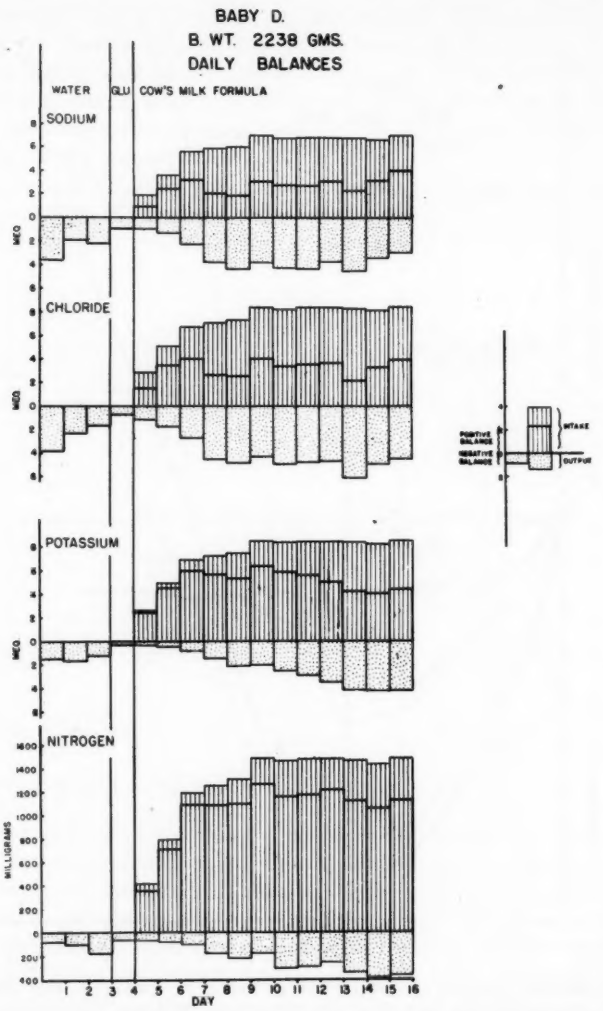

CHART IV. Daily balances, Infant 11, for 16 days after birth. First 10 days are shown cumulatively in Chart III.

during which he was studied. It is noteworthy that the urine output before food was given was about three times that of the other nonedematous infants (22.4 ml./sq.m./hr.). The N and K losses, and the retention of all elements when food was given, were generally similar to the pattern in nonedematous infants not given water. However, the Na and Cl losses were increased over what might have been expected had no water been given, and the serum values of Na in this baby showed little rise (Table III). Calculation by the Darrow method[15] shows that about 47% of the water loss was from intracellular fluid, whereas in Infant 3 (Chart I) a similar calculation shows that the

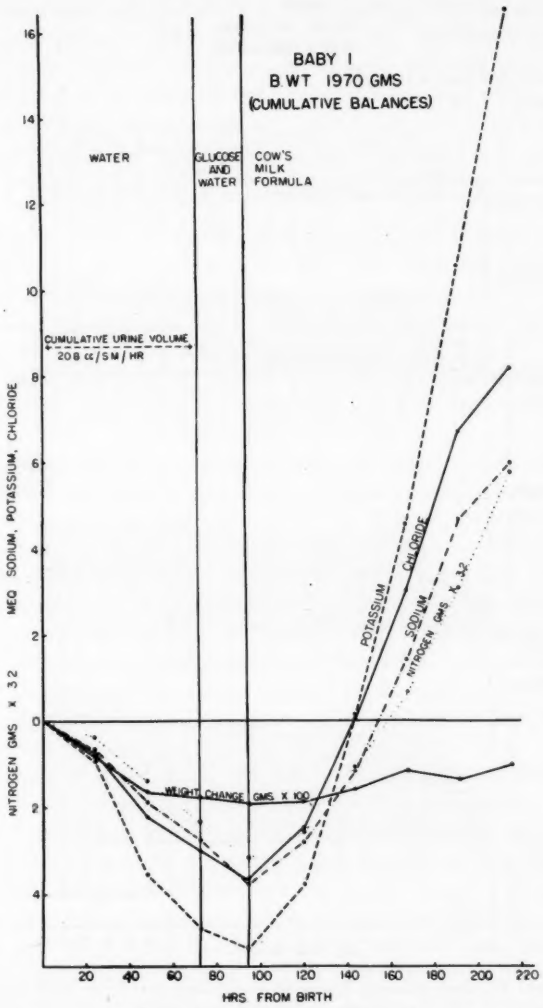

CHART V. Cumulative balances and weight change, Infant 12, during 10 days after birth. Moderately edematous infant who was given water freely from 16 hours. Balance data are presented as daily amounts in Chart VI.

intracellular fluid furnished 68% of the water lost. It would seem then, that the supply of water by mouth in this baby at least permitted a limitation in the loss of intracellular fluid similar to that shown by Gamble for fasting adults.[16]

Chart IV throws some light on the retention of K. It portrays the daily rather than cumulative balances of the infant under dissussion, its first portion repeating the data presented cumulatively in Chart III, but the results are carried on through the entire 16 days of collection. It is here apparent that although Na, Cl, and N retentions, when once

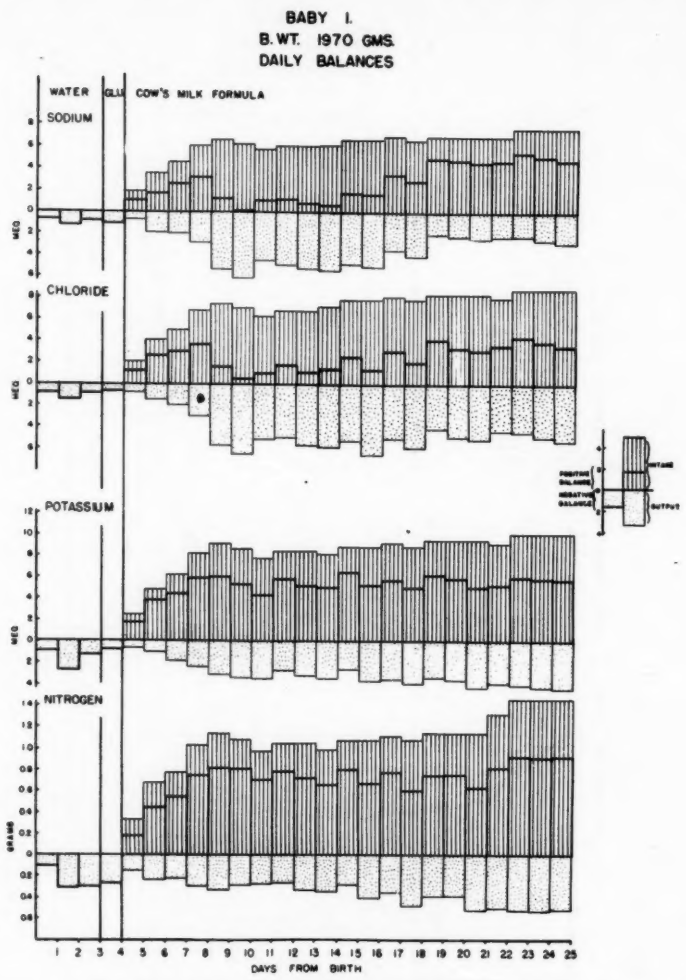

CHART VI. Daily balances, Infant 12, for 25 days after birth. First 10 days are shown cumulatively in Chart V.

established at the sixth or seventh day, were fairly steady; the K balances behaved quite differently. After the initial negative balances, a marked retention of K occurred, which continued for eight to nine days with a correspondingly small output in the urines. On the 12th and 13th day after birth, the retention dropped fairly suddenly and remained almost constant for the last three remaining days of observation, when K and N were being retained as in orderly growth of body tissue. In this baby about 12 mEq. of K in excess of an estimated requirement for growth were retained during the first 12 days of life, which presumably indicates a deficiency at birth.

In the second baby who was given water from 16 hours after birth, collections and

balance studies were continued for 25 days. The cumulative balances for the first 10 of these are shown in Chart V. Although this infant was edematous, his urine output before food was given (20.8 cc./sq.m./hr.) was actually less than that of the previous and nonedematous infant of Charts III and IV, and his Na and Cl losses were also less. On the other hand, the N and K losses were more in keeping with those in the other edematous infants. Following the provision of food, Na and Cl as well as N and K were promptly retained. Clinically, the baby remained somewhat edematous throughout this period.

This infant thus displayed an early loss of N resembling that found in other edematous babies and reflected in the blood urea values (see Table IV), but failed to show early excretion of the anticipated amounts of Na and Cl. Similarly, low outputs of Na and Cl in the presence of increased loss of N from body protein occurred in Infants 5 and 8 Table II. All infants with this dissociation were clinically edematous for some days. It would seem that this peculiar and unexplained persistence of edema with delayed output of Na and Cl is a not uncommon variant of the adjustment after premature birth.

The balances for the entire 25 days of collection are shown in daily amounts in Chart VI. Following the early retention of Na and Cl already described, there was a period from about the ninth to the 16th day when very little of these two elements were retained and when the excretion in the urine was high. Relatively excessive K retention continued unchanged. Subsequently Na and Cl retention increased to about 2 to 3 mEq./day. The retention of N was only about 60 to 65% of intake compared with that of the preceding infant (Chart IV) who retained about 80% of the N given, and this is not entirely accountable for by the difference in weight. It probably represents a continuation of the increased breakdown of body protein shown by edematous infants. During the last few days N retention relative to K increased so that the ratio, though still high, began to approach that found in normal cell fluid.

The weight changes of Infant 12 reflected the balances just described. There was a loss of about 190 gm. before food was given and this was followed by a gain in weight for three days. During the period when Na and Cl balances were small, the weight remained almost stationary and when retention began again (at about 16 days) the weight increased steadily. The conclusion seems inescapable that the small losses of Na and Cl in the thirsting period and the retention of Na and Cl immediately after food was given represented an attempt to retain the edema for an unusually long period after birth. Indeed, clinical edema did not finally disappear until the ninth day of life. For this delayed disappearance of edema, accompanied as it was by the appropriate changes in weight and in Na and Cl balances mentioned above, we have no satisfactory explanation. It is unlikely that it was related to the administration of excess water to this particular infant, for there was a similarly late loss of edema in Infants 5 and 8 who were denied water. We assume that the similar small losses of Na and Cl shown in Table II for Infants 5 and 8 were followed by a later phase of poor retention which would have revealed itself had their balance studies been sufficiently prolonged. Altogether, the evidence suggests that the results in Infants 1 to 10 were not primarily determined by the lack of water intake.

In summary, the following features were shown by all the edematous babies studied: 1. an excess of Na and Cl which begins to be discarded either immediately after birth or

after a delay of a few days; 2. a deficiency of K as indicated by a relatively excessive retention of this element when food is given; 3. and an increased breakdown of body protein following birth, reflected by a greater loss of N during fasting, a greater rise in blood urea, and, perhaps, a lessened retention of N from the food. This increased breakdown of body protein has always promptly followed birth, even when loss of Na and Cl was delayed for some days.

While infants not clinically edematous have not shown large losses of Na and Cl, their retentions of Na have been so low as to suggest an excess of intracellular Na at birth. The fact that even these babies show a retention of K in excess of N for some time following feeding suggests that the processes we have described in all 12 infants differ in degree rather than in kind and that the edema shown by certain of them may well be an elevation above the clinical horizon of an underlying tendency common to all. Although the difference between premature and full term infants with respect to all these findings is a matter for further study, the relative infrequency of edema after full term birth is worthy of remark.

It seems important to emphasize that the manifestations shown by the edematous babies were not related to any evidence of stress during labor. Moreover, since the maximal concentrations of urine were similar in the edematous and nonedematous infants and since Na and Cl outputs were sometimes low while N excretion was high, it seems unlikely that edema following premature birth is caused directly by a deficiency in renal function. On the whole, it seems to us that the features, which characterize the water, N, K, Na, and Cl alterations of premature infants and which are exaggerated in the edematous ones, are probably related to endocrinologic processes occurring in the mother and fetus during the last part of pregnancy and suddenly altered at birth. Elucidation of the exact mechanism must obviously await further investigation but in view of the resemblance between the features described and those following withdrawal of desoxycorticosterone administered to experimental animals,[17, 18] it is interesting to consider the large size of the fetal adrenal cortex and its degeneration at or soon after birth.[19]

Summary

Many premature infants are born with an edema which is probably the expression of a physiologic mechanism common to all and intensified in some. Clinical observation has shown this to be a disabling condition and prejudicial to survival. Measures which assist its removal, if otherwise safe, may be advantageous even to prematures in whom edema is not severe enough to be visible. Conversely, procedures likely to augment an edema already present might tend to produce it in nonedematous babies.

This investigation has shown an association between manifest edema, an increased breakdown of body protein, and relatively large amounts of Na and K in the urine. All these changes characterize the phase between birth and feeding. Whether or not edema is present, K is rapidly reaccumulated when feeding is begun, and its replenishment reaches an amount considerably above that present at birth. Disappearance of the edema is accompanied by losses of Na and Cl. These alterations occur whether or not water is administered and are ultimately proportional to the amount of edema originally present. Edema usually clears in a day or two but may occasionally persist for a week or more. The time of its disappearance, like the mechanism of its presence, is governed by unknown, perhaps endocrinologic factors. It could not be "washed out" of the body by an increased

water intake in the one infant subjected to that procedure. There is every reason to believe its presence would be increased or prolonged by administration of sodium-containing solutions. On the other hand, since K appears to be present in relative insufficiency at premature birth, we propose to investigate the possible advantages of providing added K in early feedings. The clinical implications of the N balances are not clear.

In this clinic, the problem is at present met by allowing no intake whatever for as long as four days after birth, the time being governed by the degree of edema. The excess body water and much of the excess Na are usually removed during this phase. Reduction of body weight by as much as 20% may occur, and the concentration of extracellular fluid becomes significantly increased. On the other hand, danger from aspiration is avoided, and when intake is ultimately begun, the organism is no longer encumbered by edema. Should it be possible in the future to facilitate readjustment of body chemistry by early oral administration of specially designed solutions, the resultant advantages would still have to be weighed against the aspiration hazard.

Acknowledgements

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SPANISH ABSTRACT

Ajuste de Electrolitos y Agua Despues de un Nacimiento Prematuro (Con Especial Referencia al Edema)

Esta investigación demuestra una asociación entre el edema claro y una descomposición crecida de la proteina del cuerpo conduciendo a una producción relativamente grande de N en la orina. La producción urinaria de K es también mayor en los infantes edematosos. Ya sea que el edema esté presente o no, el K se re-acumula rapidamente cuando se principia la alimentación, y su rellenamiento alcanza una cantidad considerablemente superior a la que existía al tiempo del nacimiento. La desaparición del edema viene acompañada de pérdidas de Na y Cl. Estas alteraciones suceden ya sea que se administre agua o no y quedan finalmente en proporción con la cantidad de edema presente originalmente. El edema generalmente desaparece en uno o dos días, pero muy amenudo dura una semana o más. El tiempo de su desaparición, como el mecanismo de su presencia, está gobernado por elementos desconocidos, talvez endocrinológicos. No se puede hacer desaparecer del cuerpo mediante una ingestión crecida de agua en el infante sujeto a este tratamiento. Se tiene toda la razón para creer que su presencia aumentaría o se prolongaría mediante la administración de soluciones que contengan sodio. Por otro lado, como el K parece estar presente en insuficiencia relativa en el parto prematuro, sugerimos investigar las posibles ventajas de proporcionar K adicional en las primeras alimentaciones. Las implicaciones clínicas de los equilibrios N no son claros.

En esta clínica, el problema se ha subsanado ahora no permitiendo ninguna ingestión hasta después de un período de cuatro días después del nacimiento, el tiempo depende en el grado de edema. El cuerpo de agua excesivo y mucho del exceso Na se remueven generalmente durante esta fase. Pueda ser que haya una reducción en el peso del cuerpo de un 20%, y la concentración del flúido extracelular aumenta marcadamente. Por otro lado se evita el peligro de aspiración y cuando la ingestión al fin principia, el organismo ya no está agravado por el edema. En caso de que sea posible en lo futuro facilitar el re-ajuste de la química de cuerpo mediante la temprana administración oral de soluciones preparadas especialmente, las ventajas que resultasen tendrían siempre que ser consideradas en cuanto al peligro de aspiración.

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THYMOL TURBIDITY VALUES IN THE SERA OF NEWBORN AND PREMATURE INFANTS AND OF MOTHERS AT TERM

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INTRODUCTION

DURING the course of a study of plasma proteins in premature and full term infants, the values obtained, especially from the globulin fraction, occasionally were found to vary considerably within the group. It seemed desirable to attempt to correlate these findings with studies of liver function. The thymol turbidity test of MacLagen[1] appeared to be ideal for use in small infants because of the small amount of serum (0.05 ml.) required. Since there have been no previous reports in the literature of the thymol turbidity values in infants, no normal standards were available. This study was planned, therefore, to provide normal standards for the thymol turbidity test in full term newborn and premature infants.

We have determined values for thymol turbidity on sera obtained from full term and premature infants and compared them with values obtained in normal adult controls and in mothers at term. An attempt has been made to correlate thymol turbidity with blood globulins, albumin-globulin ratios, and in the infant group, with blood bilirubin levels. The results of these studies are presented in this paper.

SUBJECTS AND METHODS

Subjects: One hundred and eight healthy infants, born of apparently well mothers, were chosen. No attempt was made to exclude infants with physiologic jaundice. Of this group, 50 were full term newborn infants aged 1 to 3 days, 19 were newborn premature infants, and 39 were premature infants who were from 5 to 60 days of age. Sixty-five apparently healthy women at term were studied. Blood was taken for study from these patients as they entered the hospital for delivery. Twenty-eight normal adults (hospital personnel and medical students) were used as controls. Two subjects were omitted from the adult normal group after the thymol turbidity level was found to be above the accepted limit of normal of four units and after other studies confirmed the presence of impaired liver function.

Methods: 1. Blood proteins: These were done on plasma in the infants and on serum in the adults. In the infant group, blood was taken from the external jugular, femoral, or scalp veins. Centrifugation was kept to a minimum to reduce the hemolysis so prevalent in the blood of newborn infants. Proteins were done by the Greenberg modification of the Kingsley procedure as described in a previous study from this laboratory by McMurray, Roe, and Sweet.[2]

2. Thymol turbidity values were obtained by the method of MacLagen[1] as modified by Shank and Hoagland.[3]

3. Bilirubin was done by the method of Evelyn and Malloy.[4]

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This study was done in part under a contract between the Office of Naval Research and the George Washington University. (Received for publication June 23, 1948.)

TABLE I

THYMOL TURBIDITY VALUES IN INFANT, NORMAL ADULT AND MATERNAL SERA

		No. of cases	Range	Mean	Standard deviation
Infants	Full term 1 to 5 days	50	0 to 1.9	0.70	±0.59
	Premature 1 to 5 days	19	0 to 2.1	0.77	±0.88
	Premature 6 to 30 days	22	0 to 1.9	0.83	±0.50
	Premature 31 to 60 days	17	0 to 1.9	0.83	±0.54
	Total	108	0 to 2.1	0.77	±0.55
Normal adults		28	0 to 3.8	1.65	±1.15
Mothers at term		65	0.7 to 4.5	2.1	±1.00

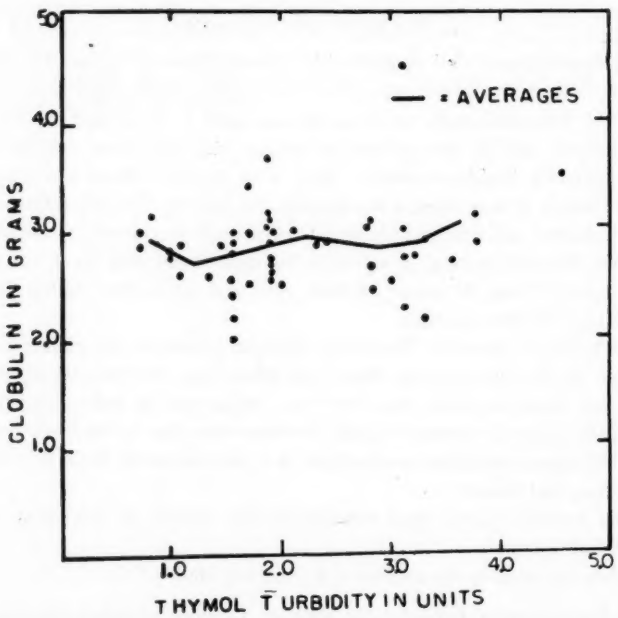

CHART I. Relation of thymol turbidity value to globulin level in sera of mothers at term. There is no correlation.

Results

Mean thymol turbidity values obtained in infants (0.77 ± 0.55), normal adults (1.65 ± 1.15), and parturient females (2.1 ± 1.00) are shown in Table I. A significant difference was observed between the infant group and the group of normal adults ($t = 5.87$).

The values obtained for newborn full term infants and premature infants up to two

TABLE II

Levels of Thymol Turbidity and Bilirubin in the Sera of Newborn Infants

	Thymol turbidity in units			
	0 to×0.4	0.5 to 0.9	1.0 to 1.4	1.5 to 1.9
Indirect bilirubin mg./100 cc.	10.00 8.10 2.60 3.40 11.30 10.40 1.60 6.60 3.10	14.8 4.3 1.44 11.83 14.40 5.20 2.00 7.40 5.80 1.34	4.42 6.20 5.80	11.43
Mean value	5.68	6.85	5.47	
Direct bilirubin mg./100 cc.	1.52 0.52 0.69 0.65 0.59 0.59 0.72 0.94 0.57	0.65 0.38 0.19 0.72 0.67 0.70 1.20 0.94 0.42 0.70	0.59 0.59 0.78	0.58
Mean value	0.75	0.66	0.65	

months of age were quite similar and no appreciable difference was noted. Maternal sera showed the highest thymol turbidity values although the difference between maternal and normal adult sera is not statistically significant in the small groups of patients studied ($t = 1.86$).

Thymal turbidity values were plotted against total globulin values and albumin-globulin ratios in the blood of both mothers and infants (Charts I, II, III and IV). No correlation could be found within either group of values.

Tests for thymol turbidity and blood bilirubin were performed on the same sample of blood in a group of 23 newborn infants 2 to 4 days of age. These are recorded in

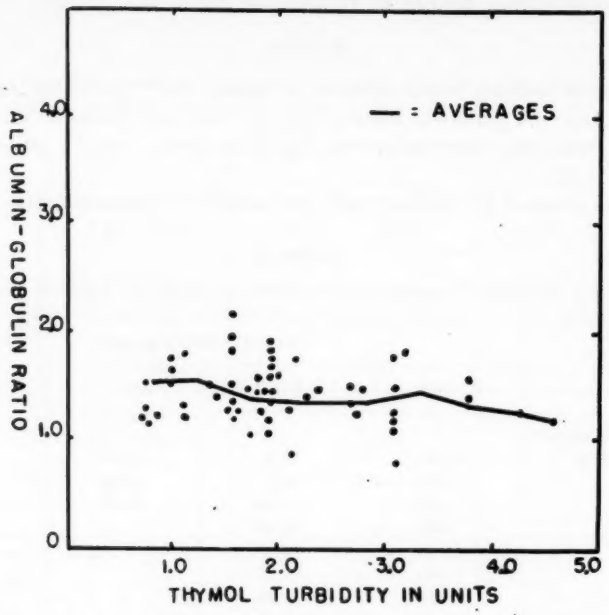

CHART II. Relation of thymol turbidity value to albumin-globulin ratio in sera of mothers at term. There is no correlation.

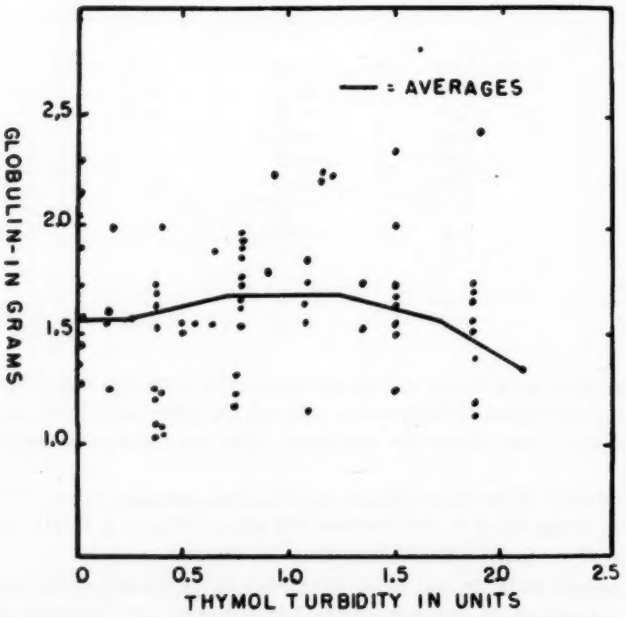

CHART III. Relation of thymol turbidity value to globulin level in blood plasma of infants. There is no correlation.

Table II. No relation could be demonstrated between the level of thymol turbidity and direct or indirect blood bilirubin.

Discussion

From the material presented above, it appears that normal full term newborn infants and premature infants of various ages have thymol turbidity values which are significantly

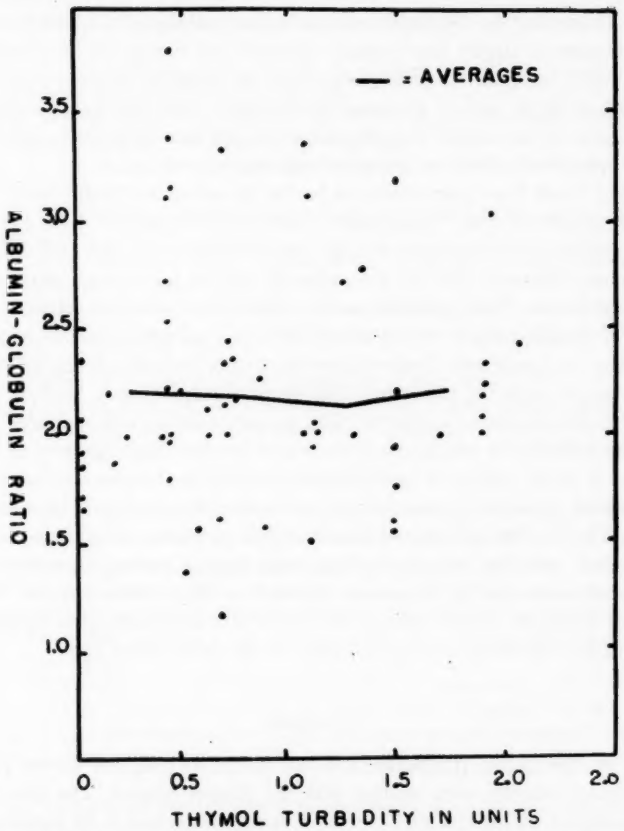

Chart IV. Relation of thymol turbidity value to albumin-globulin ratio in blood plasma of infants. There is no correlation.

below those of normal adults and mothers at term. In a group of 108 infants, only one had a value higher than two units.

There is no significant difference between full term newborn infants and premature infants up to two months of age. There is no significant correlation between the degree of total blood bilirubin found in physiologic jaundice and thymol turbidity in the newborn period. Thymol turbidity values are apparently independent of the ability of the liver to clear the blood of bilirubin when bilirubinemia is associated with physiologic jaundice only.

The low value for thymol turbidity found in infants' sera is not a reflection of a low value in the serum of mothers, as thymol turbidity values found in maternal sera are no lower; indeed, they tend to be higher, than those found in normal adult sera.

The difference between the mean values for thymol turbidity exhibited by infant sera on one hand and by the serum of normal adult and parturient women on the other is of some interest in view of recent work concerned with the nature of the thymol precipitate. Cohen and Thompson[5] by electrophoresis and ultracentrifugation demonstrated that the thymol precipitate is largely beta-globulin. Kunkel and Hoagland,[6] working with sera of patients with infectious hepatitis, state that the turbidity reaction depends on the presence both of lipids and of abnormal lipid-protein complexes migrating in the beta-globulin fraction of the serum. They demonstrated also that the gamma-globulin fraction and blood lipid level played an important role in this reaction.

Blood lipid levels have been shown to be low in infants at birth[7, 8] and elevated in the blood of mothers at term.[9] Longsworth, Curtis and Pembroke[10] made electrophoretic analyses of maternal and fetal proteins and found differences in the globulin fraction of the two groups. Maternal globulin was relatively rich in alpha- and beta-globulin with low gamma-globulin. Fetal globulin, on the other hand, was characterized by a high proportion of gamma-gobulin with relatively low beta- and alpha-globulin concentrations.

Our finding of significantly lower values for thymol turbidity in sera of infants compared to those of adults or parturient females, parallels the lower level of blood lipid and beta-globulin obtained by other workers in infant subjects. It may well be that the lower thymol turbidity of infant sera is related to low beta-globulin level or blood lipid in such sera. It is not related to total globulin or albumin-globulin ratio in infants, even though the total globulin is lower and the albumin-globulin ratio higher in this group of patients. The fact that infants, who have a high proportion of gamma-globulin, have a lower thymol turbidity than do mothers who have a lower proportion of gamma-globulin seems somewhat of a paradox in view of the observations of Kunkel and Hoagland. It would be of great interest if a series of determinations of thymol turbidity, beta-globulin and blood lipid could be done on the same infant sera.

Summary

The sera of 108 infants (premature and full term), 65 pregnant women at term, and 28 adult normal controls were studied with the thymol reagent. The mean degree of thymol turbidity of infant sera (0.77 $\pm$ 0.55 units) was found to be significantly lower than that of adult normals (1.65 $\pm$ 1.15 units) and pregnant women at term (2.1 $\pm$ 1.00 units).

No correlation could be demonstrated to exist between the absolute globulin level or albumin-globulin ratio on the one hand, and the degree of thymol turbidity in the serum of either infants or mothers at term on the other.

In the newborn group of premature and full term infants, no correlation could be found between the degree of thymol turbidity and the level of blood bilirubin as found in physiologic jaundice.

It is suggested that the low thymol turbidity values obtained in infants may be related to low blood lipids or low beta-globulin concentration as described by other authors.

ACKNOWLEDGEMENTS

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SPANISH ABSTRACT

Valores de Turbiedad Timol en Los de Recien Nacidos e Infantes Prematuros y de las Madres al Fin del Periodo

Los sueros de 108 infantes (prematuros y normales), 65 madres embarazadas al fin del período, y 28 controles normales adultos fueron estudiados con el reactivo timol. El grado medio de la turbiedad del timol en los sueros de los infantes (0.77 ± 0.55 unidades) fué significativamente más bajo que el de los adultos normales (1.65 ± 1.15 unidades) y mujeres embarazadas al fin del término (2.1 ± 1.00 unidades).

No hubo correlación entre la cantidad globulina absoluta o la proporción albumina-globulina y el grado de turbiedad del timol en el suero de los infantes o de las madres al fin del período. En el grupo de los recien nacidos—prematuros y normales, no se encontró correlación entre el grado de turbiedad del timol y la cantidad o la bilirrubina de sangre como se encontró en la inctericia fisiológica.

Los valores de turbiedad del timol obtenidos en los infantes se pueden relacionar con lípidos de sangre bajos o con la baja concentración globulina beta.

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CLINICAL OBSERVATIONS ON THE USE OF HYALURONIDASE

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THE purpose of this report is to record observations which lend support for further clinical investigation and use of the enzyme.

Original studies by Duran-Reynals[1] and McLean[2] established the fact that the injection of testicular extract subcutaneously caused a rapid dispersion of fluid or dye within the area. Chain and Duthie[3] found that the active substance of the extract was mucolytic, acting on the mucopolysaccharide, hyaluronic acid.[4-7] The spreading factor quality is derived from the fact that the enzyme hydrolyses (depolymerizes) the hyaluronic acid gel present in ground substances. This reduces the high viscosity of hyaluronic acid and removes the barrier to fluid diffusion.

Testis is the only mammalian organ in which the enzyme occurs in large amounts. Similar substances have been found in many strains of staphylococci, streptococci, pneumococci, C. Welchii, some tumors, also in snake venom, spider, bee and leech extracts. Wislocki, Bunting and Dempsey[8] have shown by metachromatic studies that hyaluronic acid is present in synovial fluid, vitreous body, Wharton's jelly, ovarian follicular fluid, nucleus pulposus, papillary layer of skin, perilobular stroma of the breast and in the stroma of the mucous membranes of the nasal cavity and the trachea. The histochemical studies of Gersh[9] seem to indicate that hyaluronic acid forms an integral part of basement membrane in various organs (kidneys, thyroid glands, etc.).

Recent reviews by Duran-Reynals[10] and Meyer[7] discuss the physiologic properties of the enzyme with relation to possible clinical application. Recently Hechter and his coworkers[11] reported the use of hyraluronidase in hypodermoclysis in a group of children.

METHOD OF STUDY

The clinical material comprises 116 infants and children. An attempt was made to include as many different types of diseases as possible, in addition to normal infants and children. The overall age of the group ranged from four days to 12 years.

The effect of hyaluronidase was observed in hypodermoclysis; after a single subcutaneous injection in infectious and noninfectious cases; in its effect on phenolsulfonphthalein excretion; and in its use in urography.

The hyaluronidase used throughout the study* was found to be very active in promoting rapid initial spreading and speedy absorption of hypodermoclyses of sodium iodide solution in animals. Both effects were clearly demonstrable by serial X-ray examination.[12]

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* This material was prepared by Wyeth, Inc. under the trade name, "Hydase," and had been tested in their laboratories. The enzyme was packaged in vials containing 0.8 mg. (1 mg. is equivalent to 150 provisional units measured by the turbidity reducing method of Kass and Seastone—J. Exper. Med. **79**:319, 1944.) of the dry (dried from the frozen state) substance or the same amount dissolved in 1 ml. of distilled water.

Effect in Hypodermoclysis

The thigh areas were used for all injections. The hypodermoclysis fluid contained 2½% of glucose and 50% physiologic saline.

Method of administration: One thigh was used for the plain saline-glucose solution (control), the other for the clysis solution plus hyaluronidase (experimental). For each solution a drip clysis apparatus with a graduated flask was used in order to regulate the speed of flow. The hyaluronidase (0.8 mg.) was introduced to the experimental area by three different methods: 1. by injecting the enzyme into the experimental area before the clysis was started, 2. by placing the enzyme in the plain glucose-saline solution on the experimental side before the clysis was started, and preferably 3. by injecting the enzyme into the tubing on the experimental side immediately after the clysis was started. The actual placing of the clysis needles into the skin was carefully supervised in order that the solutions would flow subcutaneously. Number 22 bore, 2½ inch needles were used in all procedures. The needles as well as the patient were immobilized in order to minimize mechanical interruption of the flow. The original speed of the two solutions was set at 45 to 60 drops per minute. All infants to two years of age received 125 ml. of fluid in each thigh; older children received 200 ml. of fluid in each thigh. At the beginning of each procedure the temperature, pulse and respirations were noted; they were recorded again at one hour and 24 hours. The time taken for complete absorption of the two solutions was recorded. In several cases (nine) the urine was examined at the end of the 24 and 48 hour periods. A summary of the results is recorded in Table I.

Comment

In all the cases included in this series the clysis solution plus hyaluronidase was absorbed considerably faster than the control plain saline-glucose solution without the enzyme. In 45 cases receiving both the experimental and the control solution the absorption of the hypodermoclysis was accelerated by hyaluronidase in the average from 173 minutes to 107 minutes. Thus, the acceleration amounts to about 40% and in many instances to more. Furthermore, it was not necessary to interrupt the flow of the clysis solution containing hyaluronidase because of induration or pain after it was started; whereas, with the control solution, the procedure was stopped on an average of four times because of induration, swelling and pain. At the beginning of each procedure the flow in both sides proceeded at about the same speed until 50 to 60 ml. of fluid had run in. At this point the speed of the experimental solution usually became reduced but would not stop; whereas, the control solution usually stopped at the point where tissue induration presented further absorption. A similar rate of diffusion of the experimental solution was noted in all three methods of enzyme injection. The injection of the enzyme into the tubing is preferable. In young infants the pain factor could not be evaluated; however, in older children pain was felt more in the control area.

All cases were closely observed for evidence of thermal change that could be attributed to the clysis. No such changes were noted, nor was there any evidence of reactivation of infection or spread of infection. Sannella,[13] who in Duran-Reynals' laboratory first used the enzyme experimentally in hypodermoclysis, was unable to find any evidence suggesting a thermal response or accentuation of a preexisting infection. In fact, investigators have injected hyaluronidase in and around areas which had been previously prepared by injecting staphylococci, vaccinia virus and rabbit fibroma with no evidence noted of any exacerbation of the preexisting infection. Moreover, Thomas and Duran-Reynals[14] had shown that repeated injections of testicular extract into tuberculous animals had no untoward effect even in an infection of recent origin (10 days). On the contrary, the course of the disease in the treated animals was slightly milder than in the controls.

Hechter et al[11] have recently reported controlled experiments using the enzyme in hypodermoclysis in infants and children. Their results confirm the findings of Sannella[13]

TABLE I

HYPODERMOCLYSIS

Case	Ml. fluid each side	Time (min.)		Patient	Age	
		Control	Experiment			
†1	200	295	145	Normal child	2 yr.	
*2	200		109	Dehydration-Acidosis-Diarrhea	2 mo.	
3	200	100	95	Hydrocephalus	4 yr.	
4	125	45	30	Cortical Agenesis	4 mo.	
5	200	155	113	Tracheobronchitis	29 mo.	
6	200	204	85	Bronchiectasis	4 yr.	
7	100		148	Meningitis	2 mo.	Plasma Given
†8	200	245	140	Malnutrition	3 yr.	
9	150	275	145	Pneumonia	13 mo.	
10	200	420	190	Upper Respiratory Infection	2½ yr	Mechanical difficulty with needle (control)
†11	150	165	105	Malnutrition	3 mo.	
12	150	450	375	Pyloric Stenosis	6 wk.	
13	150	390	220	Pyloric Stenosis	6 wk.	
†14	200	225	110	Malnutrition	5 yr.	
15	100	54	26	Cystic dis. of Pancreas	13 mo.	
16	100	64	40	Cystic dis. of Pancreas	13 mo.	
17	75	45	28	Pyloric Stenosis	7 wk.	
†*18	250	240	70	Pneumonia-Acidosis	3 yr.	
19	250	210	60	Upper Respiratory Infection	3 yr.	
†20	200	195	100	Normal child	5 yr.	
21	125	200	150	Pyloric Stenosis	7 wk.	
22	125	210	135	Chronic Pulmonary Infection	13 mo.	
23	150	182	100	Pneumonia	3 mo.	
24	150	95	50	Diarrhea	6 mo.	
25	150	185	80	Pneumonia	8 mo.	
26	75		90	Upper Respiratory—Circulatory Collapse	24 days	Plasma given
27	125	65	48	Diarrhea	1½ mo.	
†28	150	210	125	Acute Otitis Media	2 yr.	
29	150	115	65	Tracheitis	18 mo.	
30	150	124	94	Acute Sinusitis	4 yr.	
31	125	95	70	Upper Respiratory Infection	10 mo.	
32	100	155	128	Tracheobronchitis c Tracheotomy	7 mo.	
†33	150	115	70	Hydrocephalus	4 mo.	
34	200	235	160	Acute Rheumatic Fever	7 yr.	
35	125	60	45	Normal child	2 yr.	
†36	150	162	105	Tracheobronchitis	7 yr.	
37	150	174	100	Congenital Lues	14 days	
38	150	220	145	Tracheobronchitis c Tracheotomy	2 mo.	
39	125	65	42	Celiac Disease	26 mo.	
40	150	104	65	Celiac Disease	26 mo.	
41	200	160	90	Sickle Cell Anemia	14 yr.	
42	125	57	30	Rickets	14 mo.	
*43	200		120	Severe Acidosis c Dehydration	11 mo.	Improvement in 1 hr.
44	200	245	130	Severe Acidosis	7 mo.	
45	125	72	45	Rickets	14 mo.	

* Sodium lactate added to solution.
† Showed normal urine examination at 24 hr. and 48 hr.
Control—2½% glucose in 0.425 N saline.
Experiment—2½% glucose in 0.425 N saline+8 mg. Hyaluronidase.

that 1. fluid diffusion is accelerated, and 2. thermal response or reactivation of infection could not be detected.

Although it is quite evident that hyaluronidase facilitates the flow of solution subcutaneously, the speed of flow in any one case from clinical observations seems dependent upon 1. general development of the patient, 2. state of hydration of the patient, 3. activity of the patient, 4. position of the needles in the skin, 5. original speed of the flow, and 6. type and amount of fluid given.

Plasma was used in two cases (7 and 26) which presented a picture of shock with almost inaccessible veins preventing ready intraveneous therapy. The same procedure as outlined above was used. Hyaluronidase was injected into the skin before the clysis was started. It was noted that plasma absorbed much more slowly than dextrose-saline solution, but nevertheless it was absorbed without induration; whereas, the plain plasma

TABLE II

EFFECT OF INTRAMUSCULAR INJECTION OF HYALURONIDASE
(Dose—1 ml. No change noted)

Case	Day of Illness	Initial Temp. (°C.)	Temp. (°C.) 24 hrs.	Temp. (°C.) 48 hrs.	Disease	Cont'd. to Improve	Urine
1	2	38.6	39.5	37.0	Chronic pulmonary infection	Yes	
2	3	37.1	37.0	37.0	Pneumonia	Yes	
3	4	37.1	37.2	37.0	Diarrhea	Yes	
4	3	36.6	37.0	36.6	Meningitis	Yes	
5	5	37.0	36.7	37.0	Diarrhea	Yes	
6	3	37.1	36.7	37.0	Acute otitis media	Yes	
7	2	37.8	37.2	37.1	Tracheobronchitis	Yes	
8	7	37.1	37.1	37.1	Acute sinusitis	Yes	
9	4	37.1	37.1	37.1	Acute rheumatic fever	Yes	
10	3	37.1	37.1	37.1	Tracheobronchitis	Yes	
11	Birth	37.2	37.1	37.1	Rickets	Yes	
12	Birth	37.1	37.1	37.1	Cong. lues	Yes	
13	3	38.3	38.5	38.3	Sickle cell anemia	Yes	
14	?	37.1	37.1	37.1	Celiac disease	Slight improvement	
15	5 wk.	37.7	38.3	37.4	Acute nephritis	Slight improvement	
16	Birth	37.7	37.1	37.1	Hydrocephalus and pharyngitis	Yes	
17	4	37.7	37.7	37.2	Diarrhea	Yes	
18		37.4	37.1	37.1	Normal		Neg.
19		37.0	37.0	37.0	Normal		Neg.
20		37.0	37.2	37.0	Normal		Neg.
21		37.0	36.9	37.0	Normal		Neg.
22		36.4	37.1	37.1	Normal		Neg.
23		37.0	37.0	37.0	Normal		Neg.
24		37.0	37.0	37.0	Normal		Neg.
25		37.1	36.1	37.1	Normal		Neg.
26		36.9	37.1	37.0	Normal		Neg.
27		37.0	37.0	37.0	Normal		Neg.

clysis was even slower and did produce induration when no hyaluronidase was used. Improvement in the general circulation in both cases was noted 20 to 30 minutes after the clysis was started. No thermal reaction was observed. Six to eight hours after the injections had been given, an erythema was noted locally at the injection areas which persisted for 24 hours and disappeared. The skin reaction was not associated with fever, pain, tenderness or induration.

Satisfactory clinical response was noted in Case 2 which was a two-month-old infant with infectious diarrhea and severe acidosis. The infant was admitted in shock with subnormal temperature, peripheral circulatory collapse and a CO_2 combining power of the plasma, of 11.5 mEq./1. Intravenous therapy was not attempted. A 200 ml. clysis

was started containing sixth molar sodium lactate and 2½% glucose in 50% physiologic saline. Hyaluronidase (0.8 mg.) was injected into the clysis areas. The total volume was absorbed in 109 minutes. A second CO_2 combining power of the plasma, taken two hours after the clysis had been started, was reported to be 18.5 mEq./1. The systolic blood pressure was increased to 55. The improved peripheral circulation permitted the starting of an intravenous drip. The infant continued to improve and was discharged in 10 days.

Case 43 presented a similar problem. An 11-month-old infant was admitted with pneumonia associated with cyanosis, diarrhea, dehydration, acidosis, temperature 40.0°C. rapid respiration, CO_2 combining power of the plasma, 14.5 mEq./1., and WBC 20 thousand. A lactate-glucose-saline clysis was started. Hyaluronidase was injected into the area. 200 ml. of solution was absorbed in two hours. The CO_2 combining power of the plasma rose to 21.2 mEq./1. in three hours. Cyanosis improved in an oxygen tent. With chemotherapy and subsequent intravenous therapy to maintain fluid balance, the child continued to improve and was discharged.

These two cases illustrate the importance of subcutaneous therapy. The amount and speed of absorption through the subcutaneous layers determine the efficiency of such a procedure. It would seem that the use of hyaluronidase in hypodermoclysis provides an adequate expedient for fluid absorption without enhancing any existing infection.

In nine of the cases urinalysis were recorded 24 and 48 hours after the clyses were finished. There was no evidence of renal damage noted. Speciments were examined particularly for albumin, white blood cells and casts.

Study of Possible Side Reactions Due to Hyaluronidase after a Single Injection into Infectious and Noninfectious Cases

Twenty-seven cases comprise this study which includes 10 normal children. One ml. of the hyaluronidase solution (0.8 mg.) was injected subcutaneously in the deltoid area in each case. Temperature variations were recorded for 48 hours. Urine specimens from the 10 normal children were recorded for the 24 and 48 hour period. All cases were observed for evidence of thermal change, activation or accentuation of infection. Table II contains a summary of the results.

Analysis of the cases showed no evidence of thermal activity, spread of infection or renal damage. The pathologic changes in the basement membranes covering the glomerular and tubular renal cells, observed by Gersh[6] when kidney sections were exposed to solution of hyaluronidase are unlikely to occur in the living organism because of the high dilution factor and the inactivating power of blood plasma.[7]

Effect of Hyaluronidase on Phenolsulfonphthalien Excretion

In this study of 15 normal children and five adolescents were used for a control series, and 20 other normal children were used for the experimental observations. The age of the children ranged from six to 12 years. The purpose of this procedure was to determine* whether the addition of hyaluronidase to the established technic of the phthalein excretion test would significantly change the normal percent of dye excreted or the total fluid excretion.

In the control group, the excretion test was conducted on two successive days on

* The tests were run according to the technic given in Todd and Sanford, Clinical Diagnosis by Laboratory Methods, 10th ed., 1947, p. 163.

each individual. In the experimental group, the normal test procedure was carried out on the first day; on the second day hyaluronidase (0.8 mg.) was injected subcutaneously before the dye was introduced. Urine was collected at the end of the first and second hour. The amount of dye excreted was determined in each specimen and total renal fluid excretion was recorded. The average results of the tests in the two groups are recorded in Table III.

In evaluating the two groups collectively it can be seen that there is no significant change either in dye excretion or total renal fluid excretion. It must be admitted, however, that such a test used in children has definite limitations. Full cooperation of the individual is necessary and in some of our cases the completeness of voluntary urination

TABLE III

EFFECT OF HYALURONIDASE ON PHENOLSULFONPHTHALEIN EXCRETION

Series I (20 Cases)

Total dye excreted (average)				Total fluid excreted (average)	
1st Day Without Hyaluronidase 59.2%		2d Day With Hyaluronidase 69.0%		1st Day Without Hyaluronidase	2d Day With Hyaluronidase
1st hr.	2d hr.	1st hr.	2d hr.		
37.4%	21.95%	44.75%	24.25%	279.9 ml.	206.9 ml.

* Test conducted on first day with phenolsulfonphthalein and WITHOUT hyaluronidase; test on second day, with phenolsulfonphthalein AND hyaluronidase.

***Series II* (20 cases)**

Total dye excreted (average) Without Hyaluronidase		Total fluid excreted (average) Without Hyaluronidase	
1st Day	2d Day	1st Day	2d Day
48.0%	55.5%	218.2 ml.	220.9 ml.

** Two tests conducted on consecutive days with phenolsulfonphthalein but WITHOUT hyaluronidase on both days.

could only be estimated. There were no undesirable reactions noted during the procedures.

EFFECT OF HYALURONIDASE IN UROGRAPHY

Although only two cases are included in this group, without a similar control group, the results are significant enough to warrant further clinical case study. Frequently in small infants, a pyelogram is helpful in evaluating pathology of the urinary system. The technical difficulty of injecting dye intravenously and the occasional toxicity of dye substances frequently prevent such procedures.

Since Nesbit and Douglas[15] reported satisfactory visualization in infants following the subcutaneous injection of large amounts of diluted diodrast, the possibility that hyaluronidase might produce greater absorption of the dye was considered. Neo Iopax, an iodine-containing dye, was used in the experiments.

Case 1: The patient was a 14-day-old infant with multiple fractures caused by congenital rickets. The weight was 3.4 kg. No renal pathology was suspected. A skin sensitivity test for Neo Iopax was negative. No preliminary preparation was used. Hyaluronidase (0.8 mg.) was injected subcutaneously between the scapulae. 5 ml. of Neo Iopax diluted in 20 ml. of normal saline was injected subcutaneously at the same site. (Normally, 10 to 15 ml. of the dye diluted in 50 to 75 ml. of normal saline are used for this age infant.) Roentgenograms were taken at 5, 10, 20, 30 one-hour and two-hour periods.

Case 2: The patient was a four-year-old child, weighing 19 kg., with chronic hydrocephalus. The same procedure was used as in Case 1, except that 10 ml. of Neo Iopax diluted with 40 ml. of normal saline were given. (Normally 20 ml. Neo Iopax diluted in 80 to 100 ml. normal saline are recommended.)

In both cases a check pyelogram was taken in two weeks using the normal procedure without hyaluronidase. Review of the films in the experimental procedures showed adequate dye concentration for visual interpretation. They compared favorably with the standard procedures of dye injection. Since the amount of dye injected in the experimental procedures was at least half the standard amount used, the results may have clinical application in those infants where there is a hazard of sensitization and where large volumes of diluted dye solution cannot be given. More cases must be studied before a definite dosage of dye and hyaluronidase can be suggested. As was noted in the cases with hypodermoclysis, variations in the speed and amount of absorption will depend largely upon the musculature and hydration of the patient.

Summary

The use of hyaluronidase was observed in 116 infants and children in such procedures as hypodermoclysis, phthalein excretion test and urography. Eight tenths of a milligram (0.8 mg.) of the dry substance dissolved in 1 ml. of distilled water was used as a standard amount of the enzyme for all procedures.

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Addendum

Since this manuscript was prepared we have had an opportunity to study seven additional cases with previous control urograms. Various dilutions of 35% diodrast in physiologic saline were used. Hyaluronidase (0.8 mg.) was injected subcutaneously before the dye was given in the experimental urogram. The standard dose of diodrast for subcutaneous injection is 10 to 15 ml. of a 35% solution diluted in 35 to 75 ml. of physiologic saline. When 7.5 ml. of the dye in 25 ml. of physiologic saline was used in both control and experimental urograms, adequate visualization was seen in both studies; however, the experimental urogram showed deeper contrast, better filling, and sharper markings.

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La inyección de hialuronidase en casos infecciosos y no infecciosos (27) no demostraron actividad termal, propagación de infección ni daño renal.
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THE SPEED OF THE SECONDARY IMMUNE RESPONSE TO TETANUS TOXOID WITH A REVIEW OF WAR REPORTS AND OBSERVATIONS ON SIMULTANEOUS INJECTION OF TOXOID AND ANTITOXIN

By JOHN J. MILLER, JR., M.D., MARY LOUISE RYAN, A.B. AND R. R. BEARD, M.D.
San Francisco, Calif.

DURING World War II, active immunization with tetanus toxoid in the British and American armed forces almost completely prevented the occurrence of tetanus. Whereas this disease was common in the German and Japanese troops, a total of only 30 cases occurred in Allied personnel who had received the prescribed course of immunizing injections.[1-3] The routine immunization procedures employed are listed in

TABLE I

TETANUS IN ACTIVELY IMMUNIZED PERSONNEL

Basic Immunization in:
British Army = 2 (and after 1941) 3 injections of F.T.
U. S. Army = 3 injections of F.T.
U. S. Navy = 2 unjections of A.P.T.
Routine annual boosters ordered but often omitted

On Wounding	No Further Biol. Proph.		T.A.T.		Toxoid		Total	
	C	D	C	D	C	D	C	D
Br. Army	10	9	11	2	1	0	22	11
U.S. Army	2	1			4	2	6	3
U.S. Navy	1	0			1	0	2	0
Total	13	10	11	2	6	2	30	14
Fatality rate	76.9%		18.2%		33.3%		46.7%	
	Diff. = 58.7% ± 20.5% (2.9×SE)							

(From Boyd, Long and Sartwell, and Hall)
(See references 1-3)
F.T. = fluid tetanus toxoid
A.P.T. = alum precipitated tetanus toxoid
T.A.T. = tetanus antitoxin
C = cases
D = deaths

From the Departments of Pediatrics and Public Health, Stanford University School of Medicine, San Francisco. Read before the American Pediatric Society, Quebec, May 26, 1948. (Received for publication June 29, 1948.)

Table I. In 1941 the British increased their dose for basic immunization up to the American dose of 3 injections. In 1942 they began using routine annual boosters.

An international difference of opinion exists in regard to the proper prophylactic treatment of the immunized wounded. Whereas the British routine treatment on wounding was 3000 units of antitoxin, the equivalent of our 1500 units, the U. S. Army and Navy ordered a "wound booster" of toxoid. In the first column of Table I are grouped cases occurring in men who had neither of these additional prophylactics on wounding because of circumstances beyond control. The high case fatality rate is indicative of

TABLE II

CASES OF TETANUS IN ACTIVELY IMMUNIZED PERSONNEL
U.S. Army (Long and Sartwell)—U.S. Navy (Hall)

Immunization History			Wound	Incubation Period	Outcome
Basic	Number of routine boosters	Wound booster			
3 F.T.	0	No	Gunshot abdomen	2 days	Died
3 F.T.	0	Yes	Gunshot foot	5 days	Died
3 F.T.	1	Yes	Compound fracture	6 days	Died
3 F.T.	1	No	Compound fracture	10 days	Recovered
3 F.T.	1	Yes	Gunshot foot	10 days	Recovered
3 F.T.	3	Yes	Gunshot foot	9 days	Recovered
2 A-PT.	0	No	Crushed foot	30 days	Recovered
2 A-PT.	1	Yes	Crushed toe	8 days	Recovered

The average incubation period for tetanus in non-immunized individuals not given prophylactic antitoxin is 12.8 days (in 70 cases collected by author from reports of Boyd and of Lewis).
(See references 1–4)

overwhelming intoxications. In the second column are the British cases which received antitoxin on wounding—just as if they had never been actively immunized. This procedure, indicating British reticence to trust the secondary immune response, resulted in a significant decrease in the case fatality rate. The third column shows six cases with two deaths despite the administration of a wound booster (all but one from U. S. forces).

It is necessary here to point out that only six of the 22 British cases occurred in men who had received four or more injections of toxoid—either in their basic course or as routine boosters. None of these six died. Thus, when their total dosage approached that of the U. S. Army, their case incidence also approached ours (and their case fatality rate happened to be lower).

Table II gives the basic details of the eight U. S. Army and Navy cases.[2,3] It illus-

trates three points. The incubation period of tetanus following severe wounds may be less than a week. Under such circumstances death occurred in two instances despite a wound booster. With a single exception, the eight cases had incubation periods shorter than average for tetanus. The average incubation period in nonimmunized individuals not given prophylactic antitoxin is 12.8 days.[1,4] This seeming decrease in the incubation period in actively immunized men suggests that immunization prevented tetanus from occurring after all infections except the rapidly overwhelming ones. Boyd[1] likewise observed in the British forces that "the incubation period in the actively immunized rarely exceeded 10 days."

Certain conclusions may be drawn from this extensive field experiment: 1. Active immunization against tetanus is probably more effective than any other immunization procedure. 2. Despite immunization, rare cases may occur following extensive trauma or heavy contamination. 3. Such cases have short incubation periods, often of less than a week, and may be fatal. 4. The "wound booster" under such circumstances may not exert its effect fast enough. 5. The lower over-all incidence of tetanus in the U. S. Army and Navy as compared to the British forces is probably the result of better basic immunization, reinforced by routine annual reinjections, and is probably not the result of the difference in agents employed on wounding. 6. The administration of prophylactic tetanus antitoxin to wounded immunized individuals, though seemingly illogical, may actually be life saving under conditions of severe trauma favoring short incubation periods.

This summary of the war record is presented because of the bearing it has on pediatric (and other civilian) practice. These magnificent results were obtained in men only very recently immunized. It is to be expected that we will be called upon to treat children who have not been immunized within several years and who have not had routine annual "boosters." Indeed, municipal emergency hospitals are now faced with the problem of whether to give antitoxin or toxoid to veterans who have badly contaminated wounds resulting from automobile accidents. It is, therefore, important to find and evaluate the factors on which depend a speedy response to a reinjection of toxoid.

There is little in the literature on this subject. Peshkin[5] and McBryde and Poston[6] studied the response in children to a reinjection of alum-precipitated toxoid four and five years respectively after basic immunization with alum-precipitated toxoid. All of the children (a total of 40 in the two reports) showed rises in antitoxin to at least 0.1 unit per ml. of serum seven days after the reinjection. There is evidence[7–11] to indicate that this level of circulating antitoxin is consonant with immunity in the majority of cases. Long and Sartwell[2] made similar observations in adults on the response to a reinjection of fluid toxoid four to five years after basic immunization with fluid toxoid. All of seven individuals showed rises in antitoxin to at least 0.5 unit seven days later. These workers,[2,5,6] however, reported no antitoxin determinations earlier than seven days after the booster. From the war reports we know that the first four or five days may be of crucial importance.

Factors which might conceivably affect the speed of response to a reinjection are 1. the type and adequacy of basic immunization, 2. the type and dose of toxoid used as a stimulus, 3. the time interval between completion of the basic course and the stimulus, and 4. the immunity mechanism of the individual. The last mentioned is the unknown variable which cannot be controlled.

The following studies were made on patients of the Stanford University Children's Clinic where immunization against tetanus has been carried on since 1939. Since that

time, three types of toxoid, fluid, alum-precipitated, and aluminum hydroxide-adsorbed, have been employed. The antitoxin titrations reported here were performed by us employing the mouse technic of Glenny and Stevens.[12]

Type of Toxoid Used for Basic Immunization

In Figure 1 is compared the speed of response to a reinjection in 26 children basically immunized with fluid toxoid (and reinjected with either fluid or adsorbed toxoid) with

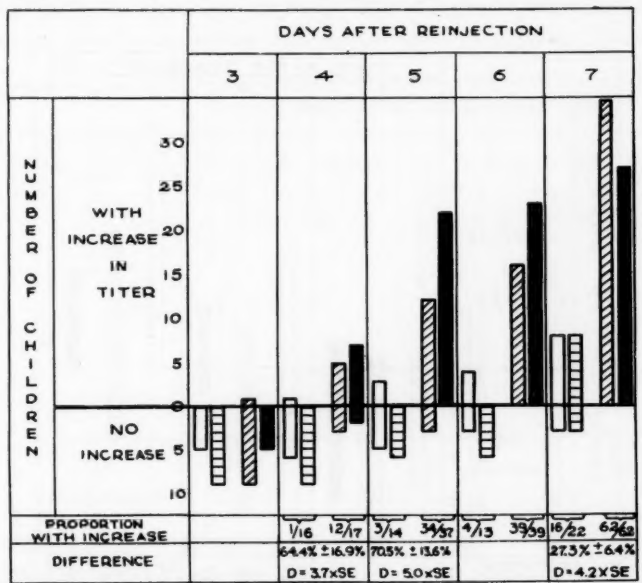


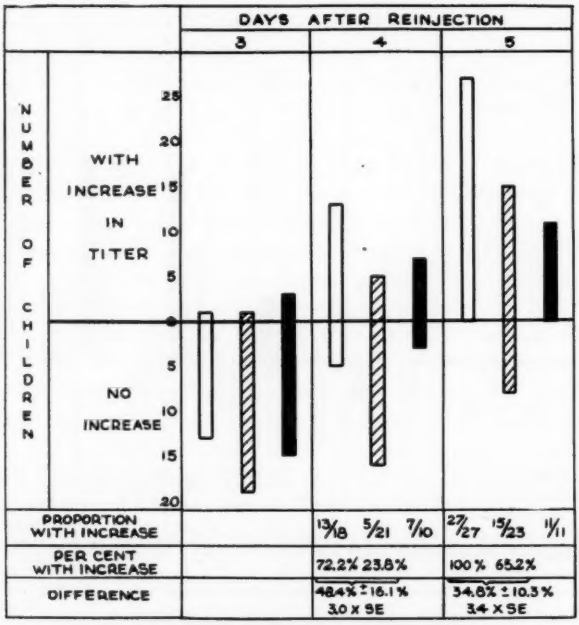
FIG. 1. 107 tests on 98 children.

that in 72 children basically immunized with adsorbed toxoid (and reinjected with either adsorbed or fluid toxoid). The two types of adsorbed toxoid which we employed, alum-precipitated and aluminum hydroxide-adsorbed, are here lumped together. A significant increase in antitoxin titer has been arbitrarily defined as an increase up to 0.1 unit antitoxin per ml. of serum if the titer was below that level, or any increase if the titer was 0.1 unit or more at the time the booster was given. The time intervals between the basic immunization and the reinjection ranged from three months to seven years. The mean time interval between the last injection of the basic course and the "booster" was actually less for children basically immunized with fluid toxoid than with adsorbed toxoid. It is quite evident from these data (Figure 1) that during the first six days after the reinjection, the majority of children basically immunized with fluid toxoid did not exhibit significant increases in tetanus antitoxin titer. Seven days after the reinjection there

were six children basically immunized with fluid toxoid whose sera contained less than 0.1 unit of antitoxin. It therefore seems quite evident that the potency of the toxoid and perhaps the type of toxoid used for basic immunization influences the speed of response to a reinjection given subsequently. The fluid toxoid which we employed provided a much poorer basic immunity than did our precipitated or adsorbed toxoid.

Type of Toxoid Used as a Stimulus

Granted a good basic immunity, does the type of toxoid used as a stimulus influence the speed of response during the subsequent week? Only children basically immunized



COMPARISON OF THE SPEED OF FLUID TOXOID ☐ A-P TOXOID ▨ AL(OH)$_3$ ADSORBED TOXOID ■ AS A "BOOSTER" IN CHILDREN BASICALLY IMMUNIZED WITH A-P TOXOID OR AL-(OH)$_3$ AD. TOXOID 1 TO 7 YEARS PREVIOUSLY

Fig. 2. 96 tests on 90 children.

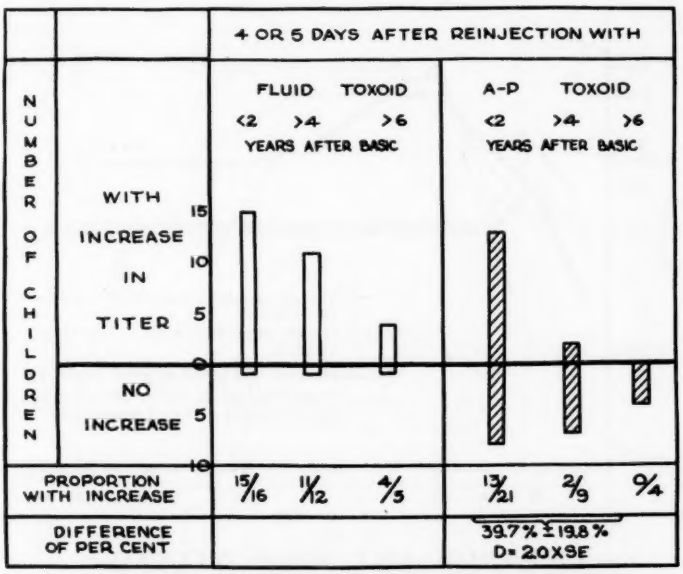
with at least two injections of alum-precipitated or aluminum hydroxide-adsorbed toxoid, and children who had at least two injections of alum-precipitated toxoid subsequent to fluid toxoid, are considered. Ninety such children were studied (see Figure 2). It is apparent that on the fourth and fifth days significantly more children reinjected with fluid toxoid showed increases in titer than did children reinjected with alum-precipitated toxoid. On the other hand, the aluminum hydroxide-adsorbed toxoid appeared to exert as prompt a stimulus as did the fluid toxoid.

Thus it is concluded that the type of toxoid used as a "booster" affects the speed of response during the week subsequent to the reinjection. As might be expected, the slowly

released alum-precipitated material is a slower acting stimulus than is fluid toxoid. Because short incubation period tetanus is the only type that need be feared in immunized children, maximum speed of response is to be sought. This would appear to be attained by basically immunizing children with adsorbed toxoids and reinjecting them with fluid toxoid when they are injured. If it is desired to use only one type of toxoid for all purposes, perhaps the aluminum hydroxide-adsorbed product is the agent of choice.

Time Interval Between Basic Immunization and Stimulus

Granted a good basic immunity, does the passage of time after basic immunization or after subsequent routine reinjections influence the speed of response? The reports of



EFFECT OF TIME INTERVAL ON SPEED OF RESPONSE

IN CHILDREN BASICALLY IMMUNIZED WITH A-P TOXOID OR $AL(OH)_3$ ADSORBED TOXOID (AND IN CHILDREN WHO HAD AT LEAST 2 INJECTIONS OF A-PT AFTER FLUID TOXOID BASIC)

Fig. 3. 58 tests on 57 children.

others quoted above[2,5,6] reveal no loss of speed up to five years though titrations earlier than the seventh day are not recorded. In Figure 3 are illustrated the responses in children reinjected in less than two years compared to those in children reinjected after four years and after six years. Fifty-seven children in these categories who were tested on the fourth or fifth day are lumped together. No children were tested on both days and the evidence is not weighted in favor of any one group. Only children basically immunized with adsorbed or precipitated toxoid, and children who had at least two injections of precipitated toxoid subsequent to fluid toxoid basic, are considered. When fluid toxoid was given them as a "booster," the passage of four and six years had no apparent effect

on the speed of response. (See Figure 3.) On the other hand, when alum-precipitated toxoid was employed as a "booster," the speed of response appeared to be delayed when the interval was greater than four years. When the interval was six to seven years, none of four children reinjected with alum-precipitated toxoid showed a rise by the fifth day (whereas four of five children injected with fluid toxoid had responded by either the fourth or fifth day). All children exhibited rises to 0.1 unit by the seventh day. The longest interval observed was seven years.

Therefore, it is concluded that a lapse of time of four years or more after completion of the basic immunization may exert a delaying effect on the response to a reinjection.

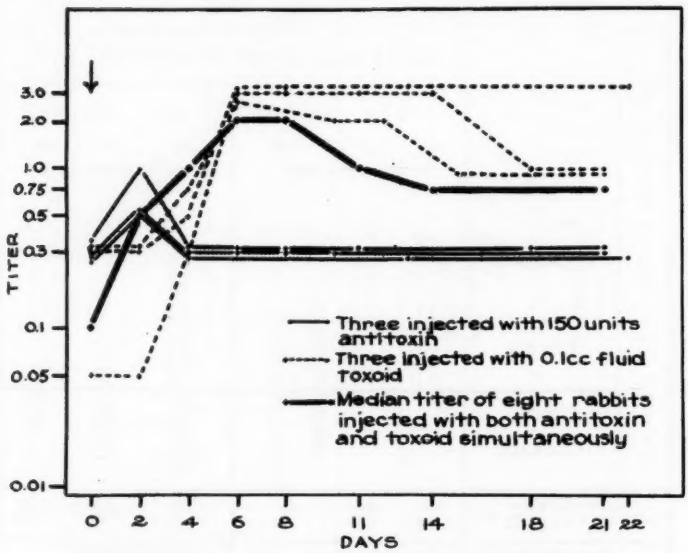


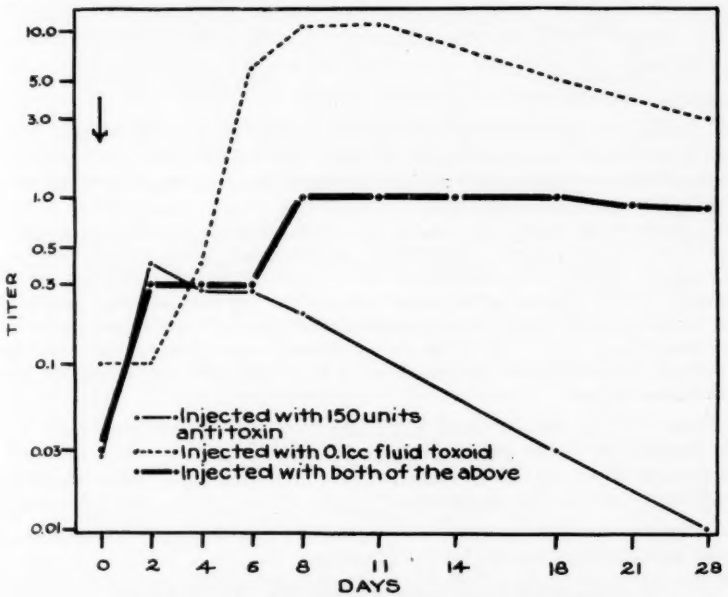
FIG. 4

It is not unreasonable to suppose that this delay may occur with any type of stimulus, but in our group it was only evident with slowly adsorbed alum-precipitated toxoid.

EFFECT OF HETEROLOGOUS ANTITOXIN

In children who had never been immunized Cooke and Jones[13] conclusively demonstrated that the administration of tetanus antitoxin interfered with the process of active immunization (the primary immune response) by inhibiting the antigenic action of toxoid. Does heterologous antitoxin (horse serum) similarly block the secondary immune response in previously immunized individuals? The writer is not aware of any studies on this point, which is highly pertinent to the problem. The following experiments were undertaken to shed light on this subject.

Experimental Evidence: Rabbits were injected with fluid tetanus toxoid. After an interval of five months three animals were injected with 150 units of tetanus antitoxin, three with 0.1 ml. of fluid tetanus toxoid, and eight with these amounts of both antitoxin and toxoid in opposite extremities. (These doses, which are one tenth the usual clinical doses, were selected because the animals weighed 3.2 to 3.6 kg.) Initial and subsequent antitoxin titrations are shown in Figure 4. In six of eight animals who received both antitoxin and toxoid, the antitoxin titer exhibited a secondary rise on or after the fourth day. This could only be due to the manufacture of additional antitoxin by the rabbits themselves, in other words, to a secondary immune response.



TETANUS ANTITOXIN TITERS (UNITS PER ML. OF SERUM) IN THREE PREVIOUSLY IMMUNIZED MONKEYS

FIG. 5

Three monkeys weighing 3.2 to 3.6 kg. were injected with 0.1 ml. alum-precipitated toxoid. Ten weeks later one was given 150 units of antitoxin, one received 0.1 ml. fluid toxoid, and the third received both agents in opposite extremities. The antitoxin titrations are shown in Figure 5. The secondary immune response in the animal receiving toxoid alone was evident on the fourth day. A secondary immune response in the animal receiving both toxoid and antitoxin appeared by the eighth day. Heterologous antitoxin delayed by four days but did not prevent manufacture of antitoxin.

Thus, in previously immunized animals, evidence is presented suggesting that the immediate protection conferred by antitoxin and the slower, greater, and more durable protection conferred by a reinjection of toxoid may frequently be elicited by the simultaneous administration of antitoxin and toxoid in opposite extremities.

Case Reports

We have observations on two children who were so treated following minor wounds.

Case 1. A two-year-old girl was brought to the clinic with a lacerated hand. Her record disclosed that she had been basically immunized with four injections of fluid toxoid, the last injection being one year previously. However, an antitoxin titration of her serum done six weeks after the fourth injection had shown less than .05 unit of antitoxin per ml. serum (the lowest amount tested for). Obviously the child was a very poor antitoxin producer. Because of this, it seemed safer to administer prophylactic antitoxin, 1500 units. One ml. of fluid toxoid was also given in the opposite extremity and blood was taken for antitoxin determinations. The results were as follows:

Day antitoxin and toxoid given	
	Less than 0.06 unit/ml. serum*
1 day later	±1.0 unit/ml. serum
3 days later	±1.0 unit/ml. serum
10 days later	±0.5 unit/ml. serum
17 days later	Less than 0.1 unit/ml. serum*

* Lowest amount tested for.

It is apparent that this child showed no secondary immune response. The decrease in antitoxin described an arc similar to that demonstrated by Bigler and Werner[9] after 1500 units of antitoxin. It is also apparent that the toxoid did not block the immediate protection conferred by the heterologous antitoxin.

Case 2. A seven-year-old boy had been basically immunized with two injections of alum-precipitated toxoid in 1941. He received a "booster" of alum-precipitated toxoid in 1942 following which he had exhibited a prompt rise in antitoxin to over 5 units. On April 1, 1948 (5½ years after his last injection), he was brought to the hospital with the startling story of having been bitten by a chicken. His immunization record was not available in the Accident Room. Fifteen hundred units of tetanus antitoxin were administered. When the boy returned to the Children's Clinic two days later blood was taken for antitoxin titration and 1.0 ml. of fluid toxoid administered. This and subsequent titrations were as follows:

2 days after 1500 units antitoxin (at the time toxoid was given)	±0.5 unit
6 days after antitoxin (4 days after toxoid)	±1.0 unit
9 days after antitoxin (7 days after toxoid)	More than 20.0 units
16 days after antitoxin (14 days after toxoid)	More than 20.0 units

This patient therefore had a secondary immune response in the presence of heterologous antitoxin and despite the long interval since his last toxoid injection.

Thus in our two cases we have conflicting results. In Case 1, did the antitoxin block the stimulus of the toxoid, or was the child a congenitally poor reactor? We knew her basic immunity was poor, and we did not regret giving her the antitoxin. It certainly did her no harm. In Case 2, the prompt secondary immune response might be ascribed to the lapse of two days between the administration of antitoxin and toxoid. However, it seems more plausible to credit the capacity to react promptly to toxoid which had been demonstrated five years previously.

On the bases of the war reports and the evidence herein submitted, the suggestion is made that maximal protection against tetanus in severely wounded immunized individuals (and when immunization occurred more than four years previously) may be obtained by the simultaneous injection of antitoxin and toxoid in different extremities. In minor wounds or scratches, on the other hand, a reinjection of toxoid alone should suffice. The fluid toxoid should be used for the reasons given above.

Summary

A review of the 30 reported cases of tetanus occurring in actively immunized personnel of the British and American armies permits the following conclusions. The only type of tetanus that need be feared in recently immunized individuals is that which may occur following extensive trauma or massive contamination. It is characterized by short

incubation periods, sometimes even less than one week, and a high case fatality rate. The reinjection of toxoid on wounding in two such instances failed to prevent death.

The speed of the antitoxin response during the week subsequent to a reinjection of tetanus toxoid was observed in a group of more than 150 actively immunized children. Marked individual differences were observed. Factors which influenced the speed of response were:

1. The type of toxoid employed in the basic immunization; alum-precipitated or aluminum hydroxide-adsorbed toxoid inducing a superior capacity to react promptly when compared to fluid toxoid.

2. The type of toxoid used for the reinjection (for the secondary stimulus); fluid toxoid inducing a more rapid rise in antitoxin than alum-precipitated toxoid.

3. The interval elapsing since the last injection of toxoid. When this interval was greater than four years the speed of response was occasionally slowed.

Experimental evidence is advanced indicating that the simultaneous injection of prophylactic antitoxin and tetanus toxoid in different extremities does not prevent the secondary immune response to the toxoid. It is therefore suggested that the maximal prophylactic effect against tetanus in severely wounded immunized individuals (and/or when immunization occurred more than four years previously) may be obtained by simultaneous injection of toxoid and antitoxin in different extremities.

Addendum

Subsequent to the presentation of this report a paper entitled, "Tetanus Antitoxin Levels in R.C.A.F. Personnel—Effectiveness of Immunization with Toxoid" was read by Dr. R. F. Farquharson at the meeting of the Aero Medical Association in Toronto, Ont., June 18, 1948. He reported that no cases of tetanus occurred during the recent war among Canadian Army personnel who had received the prescribed course of three injections of fluid tetanus toxoid (combined with typhoid vaccine). Annual recall injections and wound "boosters" were ordered.

Since this material went to press two additional cases have been observed in which both toxoid and antitoxin were administered to previously immunized wounded individuals. In both instances a secondary rise in titer in response to the toxoid was demonstrated (in one on the fourth day and in the other on the fifth day).

In a very recent article (Diaz-Rivera, R. S. et al, Penicillin in Tetanus, J.A.M.A. 138:191, 1948), new figures on the incubation period of tetanus are available. Of 51 cases in individuals who received no prophylaxis, 15 had incubation periods between one and five days. The average incubation period for the whole group was 8.4 days and for the cases with fatal outcome was 5.7 days.

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SPANISH ABSTRACT

El Progreso de la Segunda Respuesta Inmune al Toxoide Tetanos con una Revista de los Informes de la Guerra y Observaciones Sobre la Inyeccion Simultanea del Toxoide y la Antitoxina

Una revista de los 30 casos reportados de tétanos que hubieron en el personal activamente inmunizado de los ejércitos Británicos y Américanos nos permiten las siguientes conclusiones. El único tipo de tétanos al que hay que temerle en los individuos recientemente inmunizados es el que puede ocurrir después de extensa trauma o contaminación maciza. Se caracteriza por cortos períodos de incubación, algunas veces menos de una semana, y un alto tipo de mortalidad. La reinyección de toxoide en los heridos dejó de evitar la muerte en dos casos.

El progreso de la respuesta antitoxina durante la siguiente semana a la reinyección de toxoide tétanos se observó en más de 150 niños activamente inmunizados. Se observó marcada diferencia individual. Los elementos contribuyentes fueron:

1. Tipo de toxoide empleado en la inmunización básica; toxoide adsorbido en alumbre precipitado o hidróxido de aluminio indujo a una capacidad superior para reaccionar pronto cuando comparado al toxoide flúido.
2. Tipo de toxoide usado para la reinyección (para el estímulo secundario); toxoide flúido indujo a un crecimiento más rápido en antitoxina que el toxoide precipitado de alumbre.
3. El intervalo transcurrido desde la última inyección de toxoide. Cuando ésta era mayor de cuatro años el progreso de respuesta fué ocasionalmente tardado.

La prueba experimental se adelanta indicando que la inyección simultánea de antitoxina profiláctica y toxoide de tétanos en diferentes extremidades no evitó la segunda respuesta inmune al toxoide. Se sugiere, por consiguiente, que efecto profiláctico máximo contra el tétanos en individuos inmunizados heridos severamente (y/o cuando la inmunización ocurre más de cuatro años antes) se puede obtener mediante inyección simultánea de toxoide y antitoxina en las diferentes extremidades.

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THE USE OF CARONAMIDE IN PEDIATRICS

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SINCE the development of penicillin, much effort has been spent in devising ways of increasing its concentration in the blood and other body tissues, and of maintaining therapeutic levels of penicillin for prolonged periods. Part of these efforts have centered on delaying the absorption of injected penicillin, and have resulted in the development of penicillin in oil and beeswax and of procaine penicillin. Other studies have been directed towards slowing the excretion of penicillin by the kidney. Diodrast. para-aminohippuric acid and sodium benzoate all inhibit the renal excretion of penicillin, but their clinical use has proved impractical due either to the large amounts of these drugs which must be administered or to their toxic side effects.[1-3]

The most effective drug for inhibiting penicillin excretion and raising the level of penicillin in the blood is a new compound, 4′-carboxyphenylmethanesulfonanilide or caronamide. Caronamide is capable of producing a reversible inhibition of penicillin excretion by the renal tubules. And since approximately 80% of the penicillin in the urine is excreted by the renal tubules, while only 20% is eliminated by glomerular filtration,[4] caronamide can markedly elevate and prolong blood penicillin levels.

In recent months several reports have appeared describing the use of caronamide in adults. Crosson et al,[5] Shaw et al,[6] and Seeler, Wilcox and Finland[7] found that caronamide raised plasma penicillin levels significantly when penicillin was administered orally, intramuscularly, or as penicillin in oil and beeswax. Loewe et al[8] and Boger et al[9] described the clinical use of caronamide in treating subacute bacterial endocarditis in adults. Rapoport and associates[10] found that orally administered caronamide in a daily dosage of 0.2 to 0.4 gm./kg. body weight elevated plasma penicillin levels in children.

The following report gives the results of a clinical study of caronamide in infants and children undertaken in the last six months at the Los Angeles Childrens Hospital. The study was prompted by the difficulties encountered in treating several infants with septicemias due to penicillin-resistant strain of Staph. aureus.

METHODS

Twenty-one infants and children ranging in age from seven days to 12 years were treated for varying periods with penicillin and caronamide. Penicillin in saline was given by intramuscular injection at 3-hour intervals to all patients. Patient #6 received small amounts of intrathecal penicillin daily, and patient #20 received penicillin aerosol at 3-hour intervals in addition to intramuscular penicillin. Caronamide* was given orally at 3-hour intervals to some patients in crushed tablet form, and to others in a 20% suspension. The latter form ('Cremostaticin') proved much easier to administer to infants. Caronamide was given in a daily dosage ranging from 0.4 to 0.8 gm./kg. body weight.

From the Childrens Hospital, Los Angeles, and the Department of Pediatrics, University of Southern California School of Medicine.

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* Caronamide was supplied through courtesy of Sharpe & Dohme, Inc., Philadelphia, Pa.

In all cases blood samples were drawn at ½ and 3-hour intervals following penicillin injections. It was felt that these times would demonstrate the maximal and minimal penicillin concentrations achieved. One or more assays were done on each patient during caronamide administration, and a control assay was obtained before or after caronamide therapy and while the same penicillin dosage was maintained. Serum penicillin levels were determined by a modification of the Rammelkamp serial dilution method,[11] using a penicillin-sensitive Str. hemolyticus, beta as the test organism. Serum caronamide levels

TABLE I

ENHANCEMENT OF PENICILLIN LEVELS BY CARONAMIDE

Patient no.	Age	Weight (kg.)	Penicillin dosage (units every 3 hours)	Caronamide daily dosage (gm./kg.)	Serum caronamide level (mg./100 cc.)	Serum penicillin levels, units/cc			
						½ hr. after injection		3 hr. after injection	
						Control	on caronamide	Control	on caronamide
1	2½ yr.	10	100,000	0.4	—	16	8	1	2
2	2 yr.	12	100,000	0.4	—	32	64	0.25	2
3	1½ yr	12	100,000	0.4	—	8	32	0.25	1
4	2 mo.	4	40,000	0.4	—	4	16	0.06	0.5
5	10½ yr.	28	50,000	0.6	56	2	4	0*	2
6	3 wk.	3	30,000	0.5	11	16	64	0.06	2
7	2 yr.	9	50,000	0.6	8	4	16	0*	4
8	2 wk.	5	50,000	0.6	64	128	64	2	16
9	12½ yr.	45	50,000	0.5	36	2	2	0.25	0.5
10	7½ yr.	29	50,000	0.5	47	4	8	0.25	2
11	5½ yr.	17	200,000	0.5	14	16	128	2	8
				0.7	23		32		8
12	4½ yr.	15	100,000	0.5	12	4	8	0.5	4
13	2 wk.	3	100,000	0.6	15	128	128	8	16
14	3 yr.	20	50,000	0.4	8	0.5	8	0.125	4
15	1 wk.	4	100,000	0.5	25	128	256	4	128
	4 wk.			0.6	53		128		32
16	2 mo.	5	100,000	0.8	32	64	32	2	8
17	1 wk.	3.5	100,000	0.7	31	64	128	4	32
18	2 mo.	3	100,000	0.8	31	64	256	4	32
19	3 mo.	4.5	50,000	0.8	41	4	32	0*	2
20	7 yr.	22	100,000**	0.7	34	8	16	0.03	2
21	8 mo.	10	50,000	0.8	—	4	16	0.03	2

* Less than 0.03 units/cc.
** Also received 50,000 units penicillin aerosol every 3 hours.

were determined by the colorimetric method described by Ziegler and Sprague.[12] Phenolsulfonphthalein excretion tests were obtained on most patients during caronamide administration, and immediately following its discontinuance. Urine specimens for these tests were collected by indwelling catheter.

RESULTS

Twenty-one infants and children ranging in age from the newborn period to 12 years were given caronamide. In about half of these patients there was thought to be a definite clinical indication for maintaining very high blood penicillin levels. The remaining patients received caronamide in the course of penicillin therapy for less severe infections, simply to assay the effect of caronamide. Table I shows the increases in ½-hour and 3-hour serum penicillin levels obtained during caronamide administration, as well as the dosage of caronamide used and the resulting serum caronamide concentrations. The

maximal or ½-hour penicillin levels were usually increased 2- to 4-fold on caronamide, although the range of increase varied from none to 16-fold. The minimal or 3-hour penicillin levels showed on caronamide an average 16-fold increase, with the range of increase varying from 2-fold to 128-fold.

Good enhancement of the serum penicillin level was obtained with all doses of caronamide used; and there seemed to be no correlation between the serum caronamide level and the rise in penicillin concentration. This occurred although on-caronamide penicillin

TABLE II

REVERSIBLE EFFECT OF CARONAMIDE ON PHENOL RED EXCRETION

Patient no.	Age	Serum caronamide level (mg./100 cc.)	PSP test on caronamide (% excreted in 2 hours)	PSP test after caronamide discontinued (% excreted in 2 hours)
2	2 yr.		67	
3	1½ yr.		67	
5	10½ yr.	56	30	71
6	3 wk.	11	42	71
7	2 yr.	8	17	73
8	2 wk.	64	13	68
9	12¼ yr.	36	36	51
10	7½ yr.	47	24	64
11	5½ yr.	23	49	77
12	4½ yr.	12	71	
13	2 wk.	15	37	76
14	3 yr.	8	37	50
15	1 wk.	25	35	76
16	2 mo.	18	20	66
17	1 wk.	31	45	70
18	2 mo.	31	27	79
19	3 mo.	30	22	63
20	7 mo.	34	17	
21	8 mo.		18	70

levels and serum caronamide levels were determined on the same samples of blood. Where serum caronamide concentrations of 20 to 30 mg./100 cc. have been considered optimal in adults,[9] concentrations as low as 8 mg./100 cc. raised penicillin levels significantly in these children.

In the course of the study it was observed that infants treated in the newborn period showed unusually high penicillin levels. When on-caronamide penicillin levels were obtained one or more weeks later than the off-caronamide controls, there was often an unspectacular rise in penicillin level or no rise at all. Presumably this phenomenon is explained by the gradual increase in the number of functioning nephrons in the first weeks after birth, and corresponding increased ability of the kidneys to excrete penicillin.

TOXICITY

No evidence of serious toxic effect of caronamide was discovered in these 21 infants and children. Two older children had mild nausea and vomiting which seemed to be

caused by caronamide but which stopped despite continued administration of the drug. No skin rashes occurred. Eight patients showed small amounts of a reducing substance in the urine while on caronamide. One child receiving 0.8 gm./kg. body weight of caronamide daily showed caronamide crystals in the urine. All patients showed a false positive test for urinary albumin while on caronamide. Investigation proved that the "ablumin" in the urine was merely caronamide precipitated by the acid reagents commonly used for testing for proteinuria (Exton's reagent, nitric acid, acetic acid). When urine containing caronamide but no protein was tested with Pandy's solution, no precipitation resulted.

Phenolsulfonphthalein excretion tests were performed on 19 of the patients given caronamide, both during the period of therapy, and again during the first 24 to 48 hours after discontinuing the drug. These PSP tests demonstrated a reversible inhibition of phenol red excretion by the renal tubules paralleling that of penicillin. Table II presents data illustrating this point. Five patients received caronamide continuously for more than one month, one of them for 56 days, yet in these cases also the PSP tests returned to normal within a few hours after caronamide was stopped. No abnormalities were observed in the urine of patients at the end of caronamide therapy, and in those who received the drug for long periods blood NPN values were normal at the end of the therapy.

Case Reports

In 12 of the patients treated with caronamide there seemed to be a particular indication for achieving high and sustained penicillin blood levels. The following are brief abstracts of these cases:

Patient 1 was a 2½-year-old child who had a chronic septicemia due to a penicillin, sulfadiazine and streptomycin-resistant Staph. aureus hemolyticus. The septicemia had lasted for 2 years, and terminally was complicated by liver abscesses and multiple foci of osteomyelitis. The organism isolated from the child grew in vitro in a penicillin concentration of 100 units/cc. Caronamide was given for 10 days, but the penicillin levels achieved were well below the in vitro sensitivity of the child's organism. There was no improvement, and death resulted shortly.

Patient 2 was a 2-year-old child who had a chronic septicemia of 9 months' duration due to a penicillin and sulfadiazine-resistant Staph. aureus hemolyticus. There were recurrent purulent skin lesions, abscessed lymph nodes and possible liver abscesses. Staph. aureus isolated from the abscesses had an in vitro penicillin sensitivity of 100 units/cc. The child was treated for 6 weeks with caronamide, and high blood levels of penicillin were achieved (Table I). The child made an excellent recovery, and is now in good health 6 months later.

Patient 3 was an 18-month-old infant who developed a severe fulminating meningococcemia, complicated during recovery by a prolonged pericardial effusion. It was assumed, though not proved, that meningococci might be persistent in the pericardial sac, and caronamide was given for 3 weeks, with a 4-fold enhancement of penicillin levels. The child made a slow but complete recovery.

Patient 6 was a 3-week-old infant with a staphylococcal meningitis. Caronamide was given for 3 weeks, along with intramuscular and intrathecal penicillin; high serum penicillin levels were obtained (Table I). The infant recovered from the meningitis but developed a residual hydrocephalus.

Patient 8 was a 2-week-old infant who developed a septicemia in the newborn period. Staph. aureus hemolyticus and Str. nonhemolyticus, gamma were isolated from the blood stream. Their in vitro penicillin sensitivities were respectively 12.5 units/cc. and 6.25 units/cc. The infant was given penicillin in high dosage plus caronamide for two weeks, with achievement of a minimum (3-hour) penicillin level of 16 units/cc. Recovery was prompt.

Patient 11 was a 5½-year-old child with tricuspid atresia and a super-imposed subacute bacterial endocarditis. He had been twice treated with inadequate courses of penicillin during the first 2 months of his illness. The causative organism was not recovered from the blood, perhaps due to prior repressive penicillin therapy. However, the diagnosis of subacute bacterial endocarditis seemed highly

probable in view of continued fever, numerous crops of petechiae, one episode of cerebral embolization, a changing character to the cardiac murmur, and rapid weight loss. Massive intramuscular penicillin therapy (200,000 units every 3 hours) and caronamide were instituted at a time when the child was moribund, and were continued for 8 weeks. Minimum (3-hour) serum penicillin levels of 8 units/cc. were obtained. The child improved steadily on this regime, and while it is too soon to say what the ultimate outcome will be, he is now clinically well 3 months after discontinuance of therapy, and is ready for reparative cardiac surgery.

Patient 13 was a 2-week-old infant who shortly after birth developed a septicemia which was treated at another hospital with inadequate amounts of penicillin and sulfadiazine. Blood culture at the beginning of penicillin and caronamide therapy showed Str. nonhemolyticus, gamma with an in vitro penicillin sensitivity of 100 units/cc., and a Staph. aureus hemolyticus which grew in vitro in a penicillin concentration of 100 units/cc. Penicillin and caronamide were given for 6 weeks. The gamma streptococcus disappeared from the blood stream promptly, while Staph. aureus was recovered from blood cultures as late as the 23rd day of intensive therapy. Eventually the infant made a complete recovery, and is still well 3 months after therapy has been stopped.

Patient 15, a 1-week-old infant, shortly after birth acquired a septicemia which was inadequately treated with penicillin. Blood culture on admission grew out Str. hemolyticus, beta with an in vitro penicillin sensitivity of 3 units cc., and a Staph. aureus hemolyticus which grew in vitro in 100 units of penicillin cc. Large amounts of penicillin boosted by caronamide were given for 4 weeks, with serum penicillin levels as high as 128 and 256 units/cc. being achieved. Therapy continued for 17 days before Staph. aureus was eliminated from the blood cultures, but the infant eventually made a complete recovery.

Patient 16, a 2-month-old infant, developed osteomyelitis of the left tibia with blood cultures repeatedly growing out Staph. aureus hemolyticus which had an in vitro penicillin sensitivity of 100 units/cc. Caronamide and penicillin were given for 3 weeks, with good blood penicillin levels being obtained. The osteomyelitis healed, the blood stream became sterile, and 11 weeks after the end of therapy the infant is thriving.

Patient 17 was a 1-week-old infant who developed a septicemia of the newborn due to Staph. aureus hemolyticus. The penicillin sensitivity of the organism was greater than 50 units/cc. Penicillin and caronamide were given for 2 weeks, very high penicillin blood levels were achieved (Table I), and the infant made a prompt recovery.

Patient 19, a 3-month-old infant, had a right pyopneumothorax, the causative organism being Staph. aureus hemolyticus. The empyema fluid was aspirated several times, but no surgical drainage was done, nor was penicillin injected into the pleural cavity. Caronamide and penicillin were given for 3 weeks with complete clearing of the empyema, and the infant is in good health 2 months later.

Patient 20, a 7-year-old child, developed a large lung abscess after a tonsillectomy. The predominant organisms in the sputum and on bronchoscopy were Staph. aureus hemolyticus, Str. nonhemolyticus, alpha and gamma, and unidentified gram-negative rod. Intramuscular penicillin and penicillin aerosol together with caronamide were given for one month, and the lung abscess has completely healed, as demonstrated both by physical signs and X-ray films of the chest.

Discussion

It is clear that caronamide given infants and children in a daily dosage of 0.4 to 0.8 gm./kg. body weight will produce marked elevations of the penicillin blood level, particularly in the minimal (3-hour) level to which the penicillin concentration falls. The degree of enhancement of penicillin levels in this series of patients was not proportionate to the serum caronamide level; whereas, in adults a serum caronamide level of 20 to 40 mg./100 cc. is reported necessary for optimal inhibition of the tubular excretion of penicillin.[13] Caronamide appears to block the renal tubular excretion not only of penicillin, but also of phenol red. Since, however, this effect is completely reversible, and since tubular excretion is believed in normal persons to play little or no part in ridding the body of metabolites, there would seem little danger of caronamide causing serious kidney damage. Indeed no evidence of renal damage or other serious toxic effects from caronamide was encountered in this series.

The rationale for using caronamide in pediatric practice would seem to be limited to producing high penicillin levels. Since the cost of penicillin is now relatively low, use of caronamide to conserve penicillin in the treatment of most infections does not seem warranted. Nor is caronamide necessary for reducing the frequency of injections, now that forms of penicillin are available which, when injected once, provide therapeutically effective penicillin blood levels for 24 hours or longer. It does, however, appear to have a place in the treatment of those infections where high penicillin blood levels are desired; namely, subacute bacterial endocarditis, infections due to relatively penicillin-resistant organisms, and infections in which penicillin must penetrate deeply through fibrin and pus to reach the offending bacteria.

Eagle[14] points out that since 50% of amorphous penicillin in the blood stream is reversibly bound to serum, one should strive for a blood penicillin concentration of two to 10 times the in vitro maximum effective concentration. However, Marshall[15] has recently pointed out that there is no proof that a sustained penicillin blood level is needed to effect the maximum number of cures. He also suggests that in vitro penicillin sensitivities cannot be applied in vivo. This is borne out by the recoveries of several septicemia patients described in this paper. In these instances the serum penicillin levels achieved were high, but still not so high as the in vitro sensitivities of the causative staphylococci.

Summary

Twenty-one infants and children received combined intramuscular penicillin and oral caronamide therapy for periods ranging up to 8 weeks. Marked increases in the maximal and minimal serum penicillin levels were regularly obtained when caronamide was given in a daily dosage of from 0.4 to 0.8 gm./kg. body weight. No relation was observed between the height of serum caronamide levels and serum penicillin levels. Caronamide was found to inhibit reversibly the tubular excretion of phenol red. No serious toxic effects of the drug were observed. Several successfully treated patients are described briefly, and a suggestion is made as to the type of pediatric case in which the use of caronamide is indicated.

Acknowledgement

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SPANISH ABSTRACT

El Uso de Caronamide en Pediatria

Se les dió penicilina intramuscular combinada y terapia caronamide oral por períodos hasta de ocho semanas a veintiún infantes y niños hospitalizados con una variedad de infecciones. Se obtuvieron regularmente marcados aumentos en las cantidades de penicilina en el suero cuando se les dió Caronamide en una dosis diaria de 0.4 a 0.8 gm./kg. peso de cuerpo. Se encontró que el Caronamide inhibe reversiblemente la excreción tubular de phenol roja. No se observaron efectos tóxicos serios. Se describen varios casos tratados con éxito; uno con complicación endocarditis bacteriana subaguda y cuatro mostrando septicemias debido a los organismos resistentes a la penicilina.

Se recomienda el uso del Caronamide en el tratamiento de infecciones donde se deseen altas cantidad de penicilina en la sangre, i.e., endocarditis bacteriana subaguda, infecciones debida a los organismos resistentes a la penicilina, e infecciones en las cuales la penicilina debe de penetrar profundamente a través de la fibrina y pus para llegar hasta la bacteria ofensiva.

4614 Sunset Blvd.

ERRATUM

POLIOMYELITIS IN FAMILIES ATTACKED BY THE DISEASE. II. The Presence, Appearance, and Persistence of Neutralizing Antibodies: August, p. 193, l. 9 should read: The appearance of paralysis, and the presence of typical lesions in the CNS of inoculated monkeys indicates that virus was not neutralized. Conversely, no evidence of illness in a monkey indicates neutralization of virus in the serum-virus mixture, particularly if the animal (a) has no demonstrable lesions in the CNS or (b) succumbs to a challenge inoculation with the same strain.

Pediatrics

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SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

EDWARDS A. PARK, M.D., *Editor*, PAUL HARPER, M.D., *Associate*

Statements appearing in this column do not necessarily reflect the opinion of the editors nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

THE two letters which follow from Dr. John K. Glen, of Houston, Tex., state with great clearness a point of view in regard to the general subject of the policy to be pursued in regard to medical care held by many physicians in the country, and shared by a large group of members of the Academy.

Of the two letters, the first is formal, and the second, received after some correspondence with the column editors, is entirely informal. We asked Dr. Glen's permission to publish the latter because we thought that it added considerably to the understanding of his position. We are glad to publish the letters, not only for the reason already stated, but because they give the editors an opportunity to clarify the policies which they have followed in the conduct of the column, and also to express their own views on the controversial issues brought up by Dr. Glen. As editors of this column we conceive it to be our special duty to promote discussion by others, but ourselves to remain in the background. We therefore welcome this opportunity to speak.

October 5, 1948

DEAR DRS. PARK AND HARPER:

"I place economy among the first and most important virtues, and public debt as the greatest of dangers to be feared. To preserve our independence, we must not let our rulers load us with perpetual debt. We must make our choice between economy and liberty, or profusion and servitude. If we run into such debts, we must be taxed in our meat and drink, in our necessities and our comforts, in our labors and in our amusements. If we can prevent the government from wasting the labors of the people under the pretense of caring for them, they will be happy. The same prudence which in private life would forbid our paying our money for unexplained projects, forbids it in the disposition of public money. We are endeavoring to reduce the government to the

practice of rigid economy to avoid burdening the people and arming the Magistrate with a patronage of money which might be used to corrupt the principles of our government."

Had I the genius which enabled Thomas Jefferson to pen the foregoing paragraph, I would approach with lighter heart this attempt to gain acceptance of your invitation to present a facet, at least, of the opposition to the I.C.H. Recommendation.

The opposition to the Recommendation comes, in the main, from numbers of the rank and file of the Academy, from about 140,000 of the physicians of the United States who are not in the Academy and from countless lay citizens who do not want the labors of the people wasted under the pretense of caring for them.

The statement in your "Introduction" in PEDIATRICS, September, 1948, that you have received "for publication" only two letters in opposition to the I.C.H. Recommendation seems intended to convey the impression that only two men oppose it. I cannot believe that the editors of this column are so detached from Academy affairs that they do not know that the I.C.H. Recommendation has accounted for more correspondence in Academy circles than has any other one action of an Academy committee. The members of the Executive Board, or those of the I.C.H. Committee could have furnished you many letters in the interest of the opposition, or could have given you the names of those who would have gladly written you "for publication" in opposition.

The reasons for the opposition to the Recommendation may be grouped under three main topics:

(1) The Recommendation was made under suspicious circumstances; its approval by the Executive Board was constitutionally but not morally authorized; its proponents have seemed to want its passage without membership approval; it was initiated and made without the approval of physicians at large.

(2) This column, along with its predecessor, "The Social Aspects of Medicine," has seemed to so favor socialism in medicine that many Academy members look upon this colmun's very apparent support of the I.C.H. Recommendation as evidence of the proposal's being a move toward socialism in medicine.

(3) It is in itself a proposal which appears to many physicians and lay people as a socialist scheme.

Topic 1

To understand the suspicion attached to the Recommendation one must understand the attitude of the rank and file members to the Academy. The vast majority of the Academy members became members because of the opportunity offered by the Academy for pediatricians to meet their fellows from all over the nation in a spirit of friendliness, and in the hope of improving themselves and their patients by an interchange of medical experience. *They did not become Academy members for the purpose of becoming embroiled in Academy or national politics.*

Most pediatricians have not been aware of nor interested in the fact that the idea of an independent pediatric organization originated in 1932 because of a political dispute between the Pediatric Section of the AMA and the House of Delegates. They have considered the Academy not as a political forum but as a body for fellowship and scientific discussion. Regardless of the original purpose of the Academy founders, the average member wants the Academy to be scientific rather than political. For this reason

the members have not insisted that the Academy's constitution be altered although the constitution makes the Academy a top-down organization.

But apparently the idea of the Academy as a political body remained in the minds of those in whose hands has rested the power to determine Academy policies. In a scientific body the top-down type of organization is best; but in a political body—particularly in America—such organization is dangerous, and suspicion attaches to it. For a political body the constitution of the American Academy of Pediatrics is wholly inadequate because it does not enforce nor even permit democracy in the determination of Academy policies.

Because the present constitution delegates to the Executive Board the authority to transact the *business* of the Academy between annual meetings, the Executive Board apparently feels that it can assume the responsibility of determining the Academy membership's political policies. The possible rejoiner here that the I.C.H. Recommendation is not political just cannot be accepted by the majority of Academy members as a valid excuse, for they must believe that a request for federal funds is always political.

The Survey project was accepted by the Academy in 1944 and a study of the teaching of pediatrics in the medical schools was begun at that time. Three years later, in December, 1947, at an annual meeting of the Academy in Dallas nothing was said about requesting federal funds for pediatric education. Yet only two months later a meeting of the Executive Board was called and the I.C.H. Recommendation was approved—constitutionally! *After* approval, copies of the Recommendation were sent, according to Dr. Hubbard's letter of transmittal, "to all heads of pediatric departments of approved medical schools and chiefs of the pediatric services of hospitals approved for residencies, as well as officers and state chairmen of the Academy, and *others whose opinions are desired.*" Only after opposition became evident were copies sent to all members. Dr. Black received his copy—and blasted!

In spite of the objections which arose to the Recommendation, neither the Executive Board nor the I.C.H. Committee has made an attempt to poll the Academy membership for an opinion on the proposal. Rather, they sent good money after bad with a "Further Statement." We were told this was done because a *few* men had objected! I feel that even now neither the Executive Board nor the I.C.H. Committee would hazard their project (now held "in abeyance") on a mail vote of Academy members—and a mail vote is the only fair way by which each Academy member may have his say.

No one pediatrician can speak authoritatively for the rank and file without a vote. In the absence of a general vote, it should be of interest to members of the Academy to know that a poll was taken of all Texas pediatricians. The result was that nine approved and 110 disapproved the Recommendation. I have had an opportunity to converse with some of the members of the Academy in Texas—and elsewhere—and find that, in general, they think the Recommendation is of such nature as to make its proponents regard it as something which will require "careful" maneuvering to "get it by."

So far as I know, the profession at large has not appointed an official spokesman to speak for all of them in regard to the Recommendation. But I have heard of such questions as the following being asked by non-members of the Academy in deliberative councils of state medical associations, "Who do these pediatricians think they are, anyway? Do they realize they have no authority to make such a Recommendation without

the consent of the other physician-citizen of the United States? Are they with the other American physicians, or for Marx?

Some of my lay friends, to whom I gave copies of the Recommendation for comment, have remarked, "Well, if your Academy wants socialistic medicine, this is the outline for a fine beginning."

Topic 2

Those who have followed "The Social Aspects of Medicine" and "The Pediatrician and the Public" have been in little doubt that the editors "favor" a great social change in medicine. Not much has been said in behalf of the virtues of private practice. You, the editors, are welcome to the opinion that private practice has no virtues. To help keep America free and permit you and all other Americans to retain the privilege of having and expressing your own opinions, I have gone into military service in two world wars. I am not criticising you therefore for having opinions or for letting them be known. But it would be refreshing to have the editors of a controversial column so edit the column that it could have some appearance of symmetry.

The Introduction to your column in September's PEDIATRICS is a typical example of the onesidedness of which I complain. In the first paragraph you made the only editorial statement really necessary. In the second paragraph you extol your champion, Dr. Valentine. He is "eminently qualified"; "his extraordinarily able and realistic presentation"—wonderful! The first and second paragraphs comprise 9 lines. Your third paragraph introduces Dr. Gamble. But, oh!, "Certain aspects of Dr. Gamble's letter require comment." Dr. Gamble "quotes incompletely from the I.C.H. Committee Report"—horrible! (Note: you also quoted incompletely when you omitted the word "advisory" before Council on Pediatric Education). And, for 26 lines, or 65% of the Introduction's space you demolish Dr. Gamble before you permit him to speak. At that, he must speak *after* the wonderful Valentine. Is it any wonder that few send you letters for publication in opposition to the I.C.H. Recommendation?

Also in the Introduction in question you use a most inauspicious phrase: "It is felt." In this case, "It is felt that the case for the opposition has not been adequately stated." The critical reader asks, "It is felt—by *whom?* Who is the deity who will determine what is 'adequate'?"

That Dr. Black's letter was a diatribe I will not deny. But the term "diatribe" does not denote untruth. As a matter of fact, Dr. Black's letter accomplished its purpose; its devastating forthrightness has done much to "hold in abeyance" the action of the I.C.H. Committee and the Executive Board, and it awakened many physicians all over the United States to the fact that the national proponents of federal medicine were changing their tactics from pushing the W-M-D bill to the promotion of federal subsidization of medical education.

The rank and file in the Academy, Dr. Park, feel justified in having suspicions about the manner in which the whole I.C.H. Recommendation deal has been and is being handled. Would you perhaps be interested in answering the questions which arise naturally in our contemplation of the affair?

1. What was the urgency in February—if there were no urgency in the preceding December?

2. Why was the Recommendation not publicized to the Academy membership *before* it was given Academy approval?

3. Is not the Recommendation so unusual, so fraught with danger, and so controversial as to require membership rather than Executive Board approval to make it an Academy policy?

4. Why hasn't a mail ballot been taken so that each member of the Academy can register approval or disapproval?

5. Why, even now, is action on the Recommendation simply "held in abeyance"?

6. Why while it *is* being "held in abeyance," does your column keep plumping for it?

7. Why is the interest of the profession at large disregarded by the Academy?

8. Why isn't the opinion of the AMA and the N.P.C. on the Recommendation publicized in your column?

9. Why were not the pertinent resolutions of the House of Delegates of the AMA publicized in your column?

10. Why is the I.C.H. Committee out of funds?

11. What is the attitude of lay contributors to the Survey?

12. Do you want us in America to have State medicine?

The proponents of the Recommendation have not seemed straightforwardly proud of the Recommendation—nor are the opponents.

Topic 3

Members of the I.C.H. Committee have written to me their assurances that the federal government will give the medical schools money with no strings attached. The United States Supreme Court has ruled that "the government has the right to regulate that which it subsidizes." I wonder if Dr. Valentine thinks the Wilson Committee can outsmart the Supreme Court.

Our rulers can give the medical schools money but not without increasing our perpetual debt and increasing the tax in our meat and drink, in our necessities and our comforts, in our labors and our amusements.

The I.C.H. Committee and its supporters argue that federal funds for pediatric education are justified because already federal funds are used for education in tuberculosis, rheumatic fever, cardiovascular diseases, and mental hygiene. We must stop that kind of thinking and that kind of argument because it leaves the door wide open for any and everyone who would possess himself of federal funds. If we think through the sequences of the argument we see the "viciousness" of which Dr. Black complained. If pediatric departments get federal funds, other medical school departments will feel justified in also asking for federal funds. As additional federal funds are expended on medical education taxes must go higher and higher thus impoverishing the endowed schools more and more. If medical departments of Universities are supported by federal funds, other University schools will soon begin asking for federal funds. If education is "improved" by federal funds at a University level, why not give federal funds to schools at all levels? If education is supported by federal funds, why not housing, transportation, communications, mining, fuel, food supply, medicine, religion, ad infinitum? Where do we stop? The answer is we stop *now*, or not at all. If we don't stop at all we will soon be living in what, in another country, we would call a socialistic state, though it is possible that the propagandists in this country would do here as propagandists do in Russia: insist that "we" have the only true democracy in the world. But, by whatever names they are called, socialist states have a nasty way of becoming police states. And

when medical schools are supported by the government, it is my guess that the government will pass "Regulations Pertaining to Medical Schools" and that soon thereafter the government will determine "the area of need" in which the products of those schools must practice—and at what salary.

In one paragraph of his letter Dr. Valentine "emotes" on the "undernourished or crippled child, the diseased or physically handicapped man or woman, etc.," and in the next abhors the emotion of a man who cries out for freedom for all children. We in the Academy are not in our entirety "the calm dispassionate scientist." We *are* seekers after truth and reason. We believe we have found and will continue to find more truth and reason if free than if submerged in socialism. When our freedom is threatened, either abroad or at home, we not only make no apologies for having honest emotions, but, thank God, we can use them to fight for what seems to us right. There is certainly no member of the Academy who is antagonistic to child health—our very lives are spent furthering it; but as adults—and American adults—we must assure our *entire* child population freedom before risking that freedom in the supposed interest of *some* sick ones.

Dr. Valentine may not think that the Recommendation's philosophy (and his) is "collectivist"; but when, in any country, there is established a policy whereby any who finds himself in financial difficulty may get funds from the common kitty—! that seems "collectivist" to me.

And so, Dr. Park, it is my feeling that a majority of the members of the Academy will think, along with the AMA, that it is medicine's duty to do the best it can in these difficult times, to try other ways to gain support for our schools before accepting "easy" federal funds, to try to keep medicine and all other private and individual state functions out of federal hands, to try to fight our way back to a place where we do not allow our rulers to make us dependent upon them for our needs. This will be the hard way, but also the free way. "We must make our choice between economy and liberty, or profusion and servitude." The opposition chooses the former.

Sincerely yours,
(signed) JOHN K. GLEN, M.D.

November 7, 1948

DEAR DR. HARPER:

Your letter of November 4 is at hand, and I want to thank you for your kindness in making your letter so long and so explanatory.

My letter, slightly redone, should be in your hands by now, and Dr. Park has informed me that it will appear in the January issue of PEDIATRICS. I am wondering still why the proponents of the I.C.H. Recommendation and its opponents are permitted to continue this argument, particularly when the letters pro and con follow each other at intervals of some four months. It is unfortunate that publication is such a complicated task. I have had a letter from Dr. Clarence Webb recently which gave me an answer or two to the questions which I asked in my letter to you and Dr. Park. You have answered another question or two, and perhaps before my letter is published I will have the answers to all the questions. I think it likely that neither the proponents or opponents feel very optimistic about an AMA Foundation to raise forty millions a year for medical education. The fact that the Executive Board holds the I.C.H.

Recommendation "in abeyance," and the continued efforts of the proponents of the Recommendation to get in good words for it upon every occasion make those of us who oppose the proposal quite conscious of the continued intent of the I.C.H. Committee and the Executive Board to ask for federal funds for pediatric education at any moment they may so desire.

There are some extremely interesting points in regard to our controversy. For instance, the Eastern seaboard which has been heralded in American history as the cradle of American liberty seems to be the area most strongly in favor of the I.C.H. Recommendation. Next, we doctors are doing the very thing which those who hope to socialize medicine would have us do: we are dividing our house. And again, we doctors of medicine seem to be doing as is everyone else: trying to save what little tradition we may from the impending mess.

Everyone who has been kind enough to write me in support of federal legislation to allocate funds for pediatric education, has mentioned the fact that such legislation must carry adequate safeguards to preserve the freedom and initiative of medical institutions. To me this is amazing thinking. I cannot see how, if the federal government or the people will not listen to the medical profession in regard to their medical problems as is suggested by the sentence beginning on line 7, page 226, of the Maryland statement, they will be any more kindly disposed to be influenced by a much smaller group of physicians placed in an advisory capacity such as is suggested under paragraph C in the Summary of the Maryland statement. You, and all of us, must realize that those in the government who are willing at the present time to give money for pediatric education are not actually giving their own money. Government servants can well afford to give away millions of dollars of other people's money with almost no strings attached, in order to place themselves in a position where they will be the sole benefactors of medical education. It is at such a time that the clamp-down occurs.

All of us in pediatrics have been struggling all of our professional lives to improve the state of child health in America. I know of practically no physician who would say that medical care is now adequate. Frankly I think the study is telling very little that was not well known before the survey was made. If I honestly thought that federal aid to pediatric education would bring a lasting benefit to progressively more children, or if I thought that the federalization of medicine would spread the benefits of medicine to more people and give everybody better service, I would make no objections to these proposals. Actually I think that federal support of medical education will lead directly to federalization of medicine, that both procedures will aid materially in making America a socialist state, a police state, and that medical care to children will not only fail to improve but will become definitely less effective than that which is now provided.

The result of last Tuesday's election makes it quite likely that we will have compulsory health insurance. I think we will most likely have federalized medicine whether we like it or not. I feel rather certain that no attempt by the physicians to go with the trend will in any measure ameliorate the effects of socialization. I think there is no question but that concerted action upon the part of physicians to oppose the federalization of medicine would be effective. There seems little doubt that the proponents of federal medicine recognize this fact. It is for this reason that it is so important to the proponents of federalized medicine that they divide our house. I see no virtue in the medical profession's taking a position of leadership toward a goal which laymen may

demand, but which when attained will leave both the laymen and the doctors farther removed from the intended objective than now, and probably entirely devoid of individual freedom.

I intend to be at the meeting of the Academy in Atlantic City this month. I am hoping to have the privilege of a chat with you concerning our differences. You and Dr. Park are for medical education at all costs while I am for retaining freedom in America at all costs. I hope we may derive a formula which will attain both objectives.

I hope Dr. Park has fully recovered from his cold and is back on the job. Please remember me to him.

With every best wish, I remain

Sincerely yours,
(signed) JOHN K. GLEN, M.D.

THE ANSWER OF THE COLUMN EDITORS

The majority of Dr. Glen's questions are directed at officers of the Academy, and the editors of this column do not possess either the knowledge or authority to reply for them. The questions directed at us we shall not answer individually, but instead will give a general statement of our view of the function of the column and of our position on the general subject of medical care.

Why was the Column started in the *Journal of Pediatrics,* the then official organ of the Academy? The original suggestion that a column on the social aspects of medicine be run was made at the Thirteenth Annual Meeting of the Academy in St. Louis, 1944. The reasons given were: first, that no medical journal in the country was then publishing a section devoted to the social aspects of medicine or kept its readers informed of the changes in medical care which were taking place the world over, and particularly in this country. Some of these changes were of momentous importance, and no medical journal in the country was at the time open to their free discussion. The *Journal of the American Medical Association* would naturally have been expected to keep the members of that great organization informed of all aspects of this most important subject and to provide opportunity for free discussion of the whole field. The fact that an open forum has not been provided where these great and controversial issues could be fully and vigorously presented for the information of the entire profession is ultimately the responsibility of all of us.

With the special object of keeping the Academy members informed in regard to developments and experiments in medical care, we published in the *Journal of Pediatrics* such articles as the statements by Professor Lichtenstein and Professor Wallgren concerning the medical care system in Sweden; the medical care program, endorsing compusory health insurance, recommended by the Canadian Medical Association to the Canadian Government; the system of state medicine in New Zealand; a series of expositions of medical care plans in operation in this country and proposals, ranging from Dr. Nichols' "Credo" to the teaching program for the rural hospitals and practitioners conducted by the Rochester Medical School and Rochester Hospitals; the Maryland and the North Carolina plans; the Permanente Health Plan in California; and many others. We did not wish to give the impression that in publishing these descriptions of health plans and various miscellaneous proposals and statements we wished to advocate either the ideas set forth or the philosophy underlying them. Our

object has been to make it possible for the members of the Academy to keep informed of the state of developments in medical care the world over. Such knowledge is essential to any intelligent decision, in favor of or against any particular proposal. We were actuated by the principle that there is no experience, good or bad, from which it is not possible to learn, and that accurate information is the only sound basis for intelligent action. We believed, and believe even more strongly now, that organized medicine has a grave responsibility because the medical profession has not been fully informed as to the current state of affairs in the field of medical care.

We had expected discussion in our Column to spring so luxuriantly that the editors of it would experience difficulty in the selection of letters and communications for publication. Moreover, we expected it to become heated and were prepared to take the consequences of open-mindedness and to be generally dragged over the coals. We have been disappointed that there has not been more discussion in the Column, particularly by those who hold the more conservative view. We attribute the failure of those who oppose change to express themselves more freely to the fact that from the very nature of their attitudes they are not as vocal as those who would like to see changes. If the letters sent to the Column have seemed weighted numerically in favor of those who desire change, it is because more such letters have been received. When we have published an article strongly advocative of one side of the question of medical care, we have often attempted to balance it with an article on the other side. For example, we attempted to balance the letter from President Valentine, of Rochester University, advocating federal support of medical education, which appeared in the September issue of PEDIATRICS, by requesting a statement from Dr. Anderson, Secretary of the Council on Medical Education of the American Medical Association. Unfortunately, the communication which Dr. Anderson most kindly furnished was received so late that it could not be published until the November issue.

We have not considered it our function to publish résumés of existing opinion or to repeat the official views of the American Medical Association. These latter are read as a matter of course by every member of the Academy as soon as published. We never conceived it to be our function to give publicity to the views of the National Physicians Committee any more than to those of the Committee of Physicians for the Improvement of Medical Care. We have refused to publish only one letter and that for the reason that the writer digressed into the field of religion. Quite aside from the question of bias, we think the Column is accomplishing its object and performing its function if it succeeds in interesting the members of the Academy in events in the social sphere of medicine, and if at the same time it succeeds in stimulating thought. If the members of the Academy will think and will base their decisions, not on emotions, but on an intelligent knowledge of the facts, any action the Academy takes will certainly be wise and right.

Dr. Glen asks if we favor "state medicine" and this makes it necessary for us to present our own viewpoint. At present a social revolution is in progress the world over. In Eastern Europe it has assumed a violent character. In France and in Italy it is still in acute flux. In Great Britain it has been and is taking place in a wide sweep, but following the orderly processes of governmental procedure to which the British are accustomed. Since this is a world movement, it has extended of course into this country. Here it is progressing more slowly than in Great Britain, but also in an entirely rational and orderly manner. It has involved and is involving here, as in England, the whole structure and operation of medical care.

The reason that medical care is a major issue in this country as elsewhere is that the scientific advances in medicine have far outstripped their practical applications. The people of America are becoming increasingly aware that there is a very superior kind of medical care which requires a highly organized service. The elaborate organization and equipment required to supply this kind of medicine is ordinarily available to the rich and to those living within reach of the great medical centers. It is now not available to great numbers of people, both because of wide separations in space, and because of its excessive cost. There is rapidly increasing evidence on every side, not only that the people know this, but that they are, in large groups, such as the C.I.O., the United Mine Workers, the farm groups and many others, organizing to obtain it, in most instances under the leadership of physicians and public health experts who are not in agreement with the present conservative attitude of organized medicine.

Few physicians would fail to agree with the general principle that every citizen is entitled to adequate medical care and the opportunity to achieve and enjoy good health. This idea has become firmly established in the public mind and tremendous pressure has developed in favor of making it a reality. At the National Health Assembly held in Washington in May, 1948, a compulsory government sickness insurance plan was vigorously supported by a group of the largest and most powerful organizations in the country, including the American Federation of Labor, the C.I.O., the Cooperative League of America, the National Women's Trade Union League, the National Farmer's Union and many other groups. It is quite clear that the issue of medical care will be decided by the people of the country as a whole and that the way in which the issue is met will depend very largely on the ability and willingness of the medical profession to work out a plan which will meet the need and at the same time provide the quality of medical service which is necessary to the success of any plan. The political party which has most firmly supported such a change was continued in power at the election held while this article was in preparation.

We believe that the resistance of organized medicine to any fundamental change and its slowness in meeting public demand for better medical care is probably the most potent factor of all in accelerating the movement. The fact that the British Medical Association, when proposals were made by the Lloyd George Government for a system of state insurance against sickness, opposed any change and gave no guidance whatever to the government in planning the system which was later adopted is an example of what opposition rather than leadership may bring about. The result of a similar policy by the medical profession of New Zealand has been disastrous. The outcome in both instances was that a defective system, in the planning of which the medical profession had no part, was set up and put into effect over its protests. Certainly the profession which has revolutionized medical education within a single generation and which has brought American medicine to its present high level, also has the ability and enthusiasm to devise a system whereby the benefits of these accomplishments will reach the entire population.

The editors of this Column were fully aware of the dangers and defects of the Murray-Wagner-Dingell Bill and, believing as we did, that the result of its passage would bring chaos to the medical service of the United States, we opposed it. This sort of opposition can, in the absence of a satisfactory counter proposal, be effective only for a limited time. The calamity of the passage of an ill-considered and poorly planned act by the Federal Congress can be avoided and a solution beneficial both to the people

and the practicing physician can be found if organized medicine will abandon its former delaying, obstructive and evasive tactics and will, not half-heartedly or reluctantly, but enthusiastically take the leadership in developing a medical care program which will provide not only the best possible service to all the people, but will preserve the priceless features of our existing system.

It is not too late for organized medicine to regain the confidence of the people and to become the directing force in medical care planning. Such planning must make modern medicine available to those who cannot get it now, in city and country, wherever they are. Such planning must also include the construction and operation of new hospitals and centers wherever needed. A beginning has been made by the Hospital Survey and Construction Act which the American Medical Association has endorsed, although it involves heavy federal subsidies to the states. The program must also include aid to medical schools, which are in critical financial condition. We are sympathetic with and do support the effort of the American Medical Association to obtain the necessary funds from private sources. But the estimated sum required is $40,000,000.00 a year! We thoroughly agree with the resolution on this subject, passed by the members of the Academy in Massachusetts and Maryland, and at the 1948 Annual Meeting in Atlantic City that "the need for professional leadership of the program to improve medical training must not be unduly delayed" and "that if sufficient private support is not obtained within a reasonable time, then legislation to allocate federal funds for this purpose should be vigorously supported; provided that such legislation contains specific safeguards to protect the freedom and initiative of physicians and of medical institutions."

The public and their political representatives have been interested chiefly in the availability and in the cost of medical services. We believe that the paramount importance of quality of care and the responsibility for the protection of such intangibles as the patient-physician relationship which has been too frequently neglected in other countries, should become the platform and goal of the medical profession in this country.

It is our view that a forthright, cooperative and altruistic attitude toward the whole problem is the chief requirement and that such an attitude will inevitably elicit public confidence so that an orderly plan can be evolved and gradually put into operation. The adoption of a positive position by the profession for the immediate improvement of medical care through better medical training will put the profession in a strategic position for future leadership.

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE handwriting is on the wall for all to see. The people of the country have elected a President who has repeatedly during his years in office and during his campaign speeches proclaimed his intention to extend social security and to establish a national health program based upon compulsory health insurance. Heretofore he has been obstructed by a Republican Congress: now, as Republican Speaker Joseph Martin has succinctly pointed out, it cannot be doubted that the President can get through any legislation he really wants.*

One of the President's close advisors is Mr. Oscar Ewing, Administrator of the large and powerful Federal Security Agency, which we can predict with reasonable assurance will soon be elevated to cabinet status. The creation of a cabinet department encompassing government activities in medicine and public health, education and social welfare gained considerable momentum in the 80th Congress. Furthermore, it is expected that the Hoover Commission created by the Republican 80th Congress will include in its report on organization of the government's executive branch the formation of such a department. A new name has already been suggested for this branch of the government: The Department of Human Resources.

Mr. Ewing has, on many occasions, made his position very clear. In a speech† delivered three days after the election he reviewed the recently published report entitled "The Nation's Health,"‡ a report which followed the National Health Assembly in point of view of time but did not in all respects follow the recommendations made by those attending the conference. In his November 5th address he stated:

> What my report proposes is to go right down the line, item by item, and set up a series of specific objectives toward which we can all work.
>
> "It proposes to institute an immediate nation-wide recruitment of doctors, dentists, nurses, sanitary engineers, and other medical personnel, so that by 1960 our medical manpower will be 40 to 50 percent above present figures—many of whom, under the proposed plan, will inevitably be attracted to rural and small town practice.
>
> "To do this it proposes to build new medical colleges, expand the facilities of the present ones, and also to establish scholarships which will enable qualified young men and women to undertake the long and expensive training which they otherwise could not afford.
>
> "It proposes during the next 10 years to increase the number of hospital beds by at least 65 percent—the maximum goal we can hope to achieve—with special emphasis on rural districts and the smaller communities.
>
> "It proposes to establish an integrated hospital system—a series of hospitals, one at least in

* The *New York Times*—November 9, 1948.

† Delivered at the 53rd Annual Conference of the Illinois Welfare Association, Peoria, Illinois, November 5, 1948.

‡ The Nation's Health, a Ten Year Program, a Report to The President by Oscar R. Ewing, Federal Security Administrator.

every State, which will embrace every kind of hospital facility from the local diagnostic clinic up to a modern fully equipped medical center, . . .

"The plan proposes to extend our public health services to the 25 percent of our population, chiefly in rural areas, which do not now have even a full-time health official, and to staff fully all public health departments and house them in modern public health centers. . . .

"It proposes to provide rehabilitation service for all the 250,000 men and women in civilian life who each year become disabled through illness or injury.

"It proposes to extend as rapidly as possible our maternal and child health service and various child welfare services in order to reach the millions of mothers and children who are cut off from these benefits.

"It proposes to double or triple the amount of Federal aid for medical and related research as quickly as necessary scientists can be trained for this purpose.

"It proposes to delve more deeply not only into such matters as cancer and diseases of the heart but into the causes of chronic invalidism and diseases of old age, and to make fuller provision for extending effective medical care to their victims.

"It proposes to focus more and more attention on mental health, promote research in the field of psychiatry, and in the mental-emotional aspects of physical illness, and to expand manpower and facilities for both preventive and curative work in this field.

"And it proposes to promote dental research and expand the facilities of the schools and public health services in caring for the teeth of our children."

How to pay for this program which Mr. Ewing himself states "would in truth constitute a modern miracle"? He answers this question as follows:

"I am not interested in national health insurance as a system in itself. I am interested only in the health of the Nation. If I have become a staunch advocate of this particular method it is because I have examined carefully all the alternatives and have yet to find a system which will do the job more effectively."

Dr. Martha Eliot has also made very clear her own position and that of the U. S. Children's Bureau. In a presidential address before the American Public Health Association on November 9th, she emphasized the gaps in present day medical care and expressed her conviction that the remedy is public taxation in order to make medical care available to all children—with no means test.

In Congress the proponents of compulsory health insurance will undoubtedly attack this controversial issue with new vigor and confidence. The Committee on Labor and Public Welfare which has interrupted—not terminated—its investigations of tax-supported prepayment of medical care may have as its Chairman Senator Thomas of Utah who introduced S. 2588, a bill to provide grants and scholarships for medical, dental, nursing and public health education. Chairmanship of the health sub-committee may be expected to be in the hands of Senator Murray (of the Murray-Wagner-Dingell Bill) or Senator Claude Pepper.

Senator Murray returned to Washington elated by the decisiveness of his reelection triumph and we are given to understand, resolved to steer a national health insurance act through Congress before spring. Senator Thomas, a doctor of philosophy, has interested himself more in elevation of the nation's educational standards than the pros and cons of tax-financed medical and hospital care, yet he has firm views on the latter too. Although holding an open mind on the subject, he is reported to look upon a national health insurance system as the most democratic and surest way of furnishing adequate medical care to all Americans, regardless of their economic status, race or color.

Upon this background it is not too difficult to predict the reception that will be given to many health bills that will be reintroduced soon after the opening of the 81st

Congress. There is every reason to believe that a bill—toned down possibly, but nevertheless a compulsory health insurance bill—will be favorably reported before the first session of the new Congress is many months old. When it reaches the House for action Dingell and others will be waiting to carry the ball. More specifically in the field of child health and welfare we may anticipate a reintroduction of a school health services bill and a new bill for the creation of a National Child Research Institute to strength the hand of the Children's Bureau in a broad program for research in child health and welfare.

JOSEPH S. WALL, M.D., *Chairman*
Committee on Legislation

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

MANAGEMENT OF THE CHILD WITH CHRONIC ASTHMA

By JEROME GLASER, M.D.
Rochester, N.Y.

THERE are no reliable statistics concerning the incidence of bronchial asthma in children. However, it is evident that asthma in childhood is not an uncommon disease. The child with chronic asthma may be considered as one with perennial attacks which have persisted despite all efforts at alleviation. The proper management of such patients is a worthy challenge to all interested in the care of children. Most of these chronic asthmatics are classified as suffering from "intrinsic" asthma. This is essentially just another way of stating that the cause of the asthma is unknown. It is generally felt, but has never been proved, that this form of allergy is due to sensitivity to bacteria or their products.

For purposes of discussion, the treatment of the child with chronic asthma may be considered under a number of headings, of which the most important are prophylaxis, environmental control, protection against infection, education, physiotherapy and psychosomatics.

PROPHYLAXIS

Prophylaxis, as the most important method of treating any disease, always deserves consideration. As early as 1930 Peshkin[1] had emphasized this in childhood with regard to bronchial asthma and in 1936 Glaser and Landau[2] first discussed the general problem of the prophylaxis of allergic disease in this age period. While many infants are potentially allergic, allergy is more likely to develop if there is or has been allergic disease in the parents or siblings. The first allergic manifestation to occur in the human being after birth is urticaria but this is commonly so mild and so fleeting that it rarely attracts attention. Commonly the first allergic or related manifestations of clinical significance are colic or pylorospasm. Atopic dermatitis (eczema) next develops and thereafter recurrent upper respiratory infections, to be followed by pollinosis or perennial allergic rhinitis. These diseases, which are often precursors of bronchial asthma, should be early and thoroughly treated although we are far from certain, as yet, whether such treatment, even if successful, will actually prevent the development of asthma.

It is well to emphasize that one of the most important steps in the prophylaxis of chronic asthma is the treatment of pollinosis (rose and hay fever). It is not generally realized that the most serious consequence of failure to treat pollinosis is the development of asthma. This does not necessarily depend upon the severity of the pollinosis as asthma very frequently follows this disease, even when mild. Curiously this is particu-

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry.

Presented at the Areal Meeting of the American Academy of Pediatrics, Buffalo, New York, April 30, 1948.

larly noticeable in patients of Italian origin. Although the antihistaminic drugs have been used for only two seasons, the evidence is that although in many instances they give almost complete symptomatic relief of pollinosis, yet they do not prevent the development of asthma as a sequel of this disease. The antihistaminics should be used in the treatment of pollinosis but specific treatment by means of the injection of appropriate pollen extracts should not be neglected.

Because most allergic diseases of adult life have their beginnings in childhood, it must be obvious that the allergist of the future will be the pediatrician and that, as I once stated[3] in what might have been an over enthusiastic remark, the internist-allergist, will ultimately deal with the end products of neglected opportunities in pediatric allergy. Space does not permit further consideration of this interesting possibility. This discussion will not be concerned with the treatment of asthmatic attacks per se but will be limited to other aspects of the management of the child with chronic asthma.

Environmental Control

The parents of such a child must be prepared to accept the fact that, as in any other chronic disease, as diabetes, for example, the whole design of family life must revolve around the afflicted child. This may not be easy. The mother, whose heart is set on loading her home with overstuffed furniture and draperies and other types of furnishings particularly likely to produce or to hold dust, and the father, whose hunting dogs are his pride and joy, must adjust themselves to the sacrifices made necessary as a result of the illness of the child.

The home must be kept as free from dust as possible. Particular attention must be paid to the child's room. Detailed directions for accomplishing this may be obtained from any manufacturer of dustproofing fabrics or from any allergist. Complete air conditioning of the houses of the future, although designed primarily for comfort by affording an even temperature with a satisfactory moisture content, and to make the work of the housewife easier by eliminating dust, will eventually be of inestimable value in the care of these patients. The preferred form of heat is hot water or steam, because heating by hot air ducts is a very effective way of stirring up dust currents. The new form of convection heating by means of pipes coiled in the floor through which heated fluid is circulated should prove ideal. The bedding in the child's room should be free from feathers and wool regardless of skin tests and also free from other allergens as may be indicated by the history and skin tests. There should be no feather pillows in the child's bedroom and preferably none in the house. The pillows should be of sponge rubber or glass fiber and covered with dustproof covers to prevent dust from settling into the fabric. For warmth the best blankets now available are made with glass fiber insulation. These are even lighter and warmer, weight for weight, than wool blankets. The problem of wool clothing is also being solved by the adoption of glass fiber insulation in cotton clothing. The child should sleep in a room which is not uncomfortably cool, certainly not below 68°. He should never get out of bed onto a cold floor in his bare feet or walk about barefooted.

It is necessary that the asthmatic child be adequately protected from the weather, even though in accomplishing this one is forced to run counter to the fashions of the times. It is important to wear a head covering unless the weather is really warm. In wet weather the feet must be properly protected by rubbers which are also useful as

protection from cold pavements. In cold weather bare legs and knees are an invitation to trouble, a fact which is often difficult to impress on the mind of the child of high school age.

Strong odors are to be avoided by the child with chronic asthma. The odor of fresh paint is a particular offender and no painting should be done while the child is in the house nor should the child return until the odor of the paint has completely disappeared. One of the most glaring of our present day social defects is the utter disregard which most smokers show for the feelings of others regarding tobacco smoke, an important and nearly always a nonspecific irritant in bronchial asthma. The family must also guard against the use of strongly scented perfumes and other toiletries. The odors of flowers, gasoline, kerosene, moth balls, and cleaning fluids must also be avoided. Occasionally a child exquisitely sensitive to a food may react with asthma to the odor of the food as has been discussed by Horesh.[4] Such foods are best kept out of the house and at least in such cases the kitchen should be provided with a ventilator to remove the odors of these foods and also such other cooking odors as may be irritant even though nonspecific.

One of the most difficult problems in environmental control is that of family pets. It may be stated categorically that there should be no animal pets with fur or feathers in the household of an allergic individual, regardless of the results of skin tests. Sensitivity to epidermoids is so easily acquired that the presence of such animals is an invitation to trouble. I have several times had the experience of seeing a child with chronic asthma clear completely following the removal or death of the family pet which had been retained against advice, usually because the child gave a negative skin test or showed no evidence of asthma on contact with the animal so that the parents felt that they might reasonably take the gamble of keeping the pet. The futility of relying on skin tests is indicated by the work of Hooker[5] which showed that different breeds of dogs may give specific skin tests for the breed but not for dogs as a whole so that to be really of significance a child should be tested with an extract of the dander of his own pet. What holds true for dogs presumably holds true for other animals as cats, chickens, etc. though probably to a lesser extent.

Climate

It is only occasionally that a family will have the choice of the climate in which they may rear their afflicted child. Our knowledge of climatotherapy is pathetically meager. The present trend of thought is that just as in the case of tuberculosis, treatment of the patient in his own community may be carried out as satisfactorily as elsewhere, provided the patient is in expert hands. It is of great significance that at the meeting of the American Academy of Allergy in St. Louis in December, 1947, the membership was urged by Schutzbank[6] of Tucson, Ariz., and Egbert[7] of El Paso, Tex., to keep their asthmatic patients at home. Interesting contributions have also been made by Dr. July Baker,[8] an American pediatrician practicing in Mexico City, which has an altitude of 7,325 feet. She has presented evidence showing that the factor of altitude alone may cause children to exihibit evidence of food allergy which may completely disappear merely on moving the child to a place of lower altitude. It is interesting that such cases have not been reported from Denver, Colo., but this is perhaps because the altitude of Denver is about 2,000 feet lower than that of Mexico City. In many instances the presumably beneficial effects of change of climate have been eventually shown to be due

to nonclimatic factors as escape from environmental allergens and psychomatic factors as disturbing situations in family life. Nevertheless, because it is perfectly obvious that many asthmatics suffer exacerbation of symptoms because of trauma from cold, dampness, sudden changes in temperature and other meteorologic factors, the search for an ideal climate still goes on. It is my practice to advise the parents of patients approaching boarding school or college age to seriously consider sending their children to institutions in the south and southwest and in some instances this has been highly successful.

Protection Against Infection

(a) *Routine Pediatric Immunizations:* It is highly important that all children receive routine prophylaxis against diphtheria, pertussis, tetanus and smallpox. This protection is especially important in the case of allergic children because the agents used in the serotherapy of diphtheria and tetanus are particularly likely to be followed by disagreeable reactions in such children. Protection against pertussis is of paramount importance because of the marked tendency of this disease to aggravate bronchial asthma when present or initiate bronchial asthma in allergic children. Pertussis in such patients is best treated with human immune globulin or with hyperimmune human serum. Asthma resulting from pertussis or other pulmonary infection is of the so-called "lung damage" type and is particularly resistant to treatment. For this reason, also, asthematic or allergic children when exposed to measles should always be given human immune globulin in an effort to modify the disease and thus avoid pulmonary complications.

While pediatricians rarely hesitate to vaccinate allergic children, except those with eczema, they are often reluctant to give prophylactic injections for fear of allergic reactions. In my experience disagreeable reactions to diphtheria, pertussis and tetanus prophylaxis are of little more frequency, if any, than in non-allergic children, and I have not hesitated in most instances to give allergic children the routinely prescribed doses. However, if one wishes to be cautious, and this is especially important where the parents are fearful of trouble because of previous disagreeable experiences following injections, a preliminary test dose of one-tenth of the usual dosage may be given and, if there are no disagreeable reactions, the dosage may be gradually increased at regular intervals until the complete dose has been administered. Immunization carried out in this manner produces just as good results in my experience as that performed according to orthodox technic.

Tetanus immunization by means of toxoid is particularly important so that the allergic child will not need to receive tetanus antitoxin in case of injury. Unfortunately, there is not now available, as formerly, tetanus antitoxin made from bovine serum,[9] and all tetanus antitoxin now manufactured in this country is derived from horse serum to which reactions are much more frequent and disagreeable. If horse serum is used, the despeciated serum is the preparation of choice but even this must be given with great care.

(b) *Protection Against Respiratory Infections:* The child with chronic asthma must be particularly protected against infections of the respiratory tract. It is the practice of most allergists to give these children a mixed respiratory vaccine. It is well known that studies in large industrial and collegiate groups have shown little or no benefit from the use of such vaccines. From these studies it cannot be assumed, however, that this treatment has no value in the case of asthmatic children who as a group are especially susceptible to respiratory infection, and most allergists are convinced that the use of such

vaccine is very much worthwhile. The literature on this subject has been reviewed by Unger.[10] There is, however, a difference of opinion as to the relative merits of stock and autogenous vaccines. In practice a combination of both may be used. Autogenous vaccines are made from nose and throat cultures, preferably taken from suspicious or definitely diseased areas and from the sputum of those relatively infrequent children who bring up sputum. I have had no experience with vaccines obtained on culture by bronchoscopy as described by Crump.[11] A stock vaccine is prepared by mixing various autogenous vaccines. The vaccine which any individual patient will use is made by adding some of his autogenous vaccine to the stock vaccine. Thus the child is treated not only with his own organisms but also receives a sample of most of the organisms present in the respiratory tract of many of the asthmatic children of the community at any given time of the year. The value of a vaccine containing a multiplicity of organisms is stressed by Ratner[12] who points out that the non-specific effect of the anamnestic reaction in some unknown manner stimulates antibody formation in general. The use of mixed autogenous vaccines as stock vaccine also eliminates the factor of attenuation of virulence which often occurs when vaccines are made from laboratory strains. I had thought when I started using this type of vaccine that this method of preparation was original but have since found that many others prepare their vaccines in a similar manner. However, one routine modification is original as far as I can discover and that is the routine addition to this vaccine of a small amount of Phase I pertussis organisms so that the asthmatic child, with each injection gets a small booster dose of pertussis vaccine. Under such circumstances pertussis rarely occurs and, when it does, is very mild.

Finke[13] has drawn attention to the possibility of infection of the child from other members of the family who suffer from chronic non-tuberculous broncho-pulmonary disease. The grandfather who has a chronic cough, which the family attributes to the use of tobacco or to "chronic catarrh," may perhaps be coughing for other reasons and this may result in pulmonary infection in the child. While this hypothesis remains to be confirmed, it seems reasonable to accept in the case of children with respiratory allergy where the mucous membranes are often edematous and a fertile field for infection.

A relatively new measure which has not been completely evaluated is the use of therapeutic aerosols, particularly penicillin. Reports on the use of such aerosols are not in complete agreement. There is also the possibility that the prolonged use of antibiotic aerosols may develop strains of bacteria resistant to the specific antibiotics employed. However, there is at least an occasional patient whose attacks follow upper respiratory infections in whom the most successful and sometimes the only method of aborting attacks of asthma is the vigorous use of penicillin aerosol immediately at the onset of the acute upper respiratory infection.

Recurrent Lymphadenoid Tissue in the Nasopharynx

The child with chronic asthma, even though under constant observation while receiving injection therapy, should have a thorough routine examination at least twice a year. At this time the course of the disease during the previous six months should be studied and an attempt made to find clues to possible as yet undisclosed factors. The study of such a child is a constant process of education of both the parent and the physician. A complete routine nose and throat examination by a specialist should be made at this time and special attention should be paid to the nasopharynx. The reason is that if excess lymphoid tissue has recurred following a primary adenotonsillectomy,

appropriate treatment of such tissue may at times result in a marked amelioration of the asthma. This is a new phase in the study of such children which has as yet by no means received the attention it should have from both the pediatrician and the allergist and is of such importance that a brief review of this subject would appear timely.

The first work in this field was done in 1938 when Crowe and his associates[14,15] reported the use of radiation in the treatment of lymphoid hyperplasia of the nasopharynx. These investigators were primarily interested in the treatment and prevention of deafness. Their studies revealed the wide distribution of lymphoid tissue in the nasopharynx in addition to the pharyngeal tonsil or adenoids.

They observed that during childhood lymphoid tissue in the throat reacts to infection by increasing in size and spreading to areas of mucous membrane normally free from it. It often happens that, after removal of the tonsils and adenoids in children and in some adults, numerous nodules of lymphoid tissue, often present but not particularly prominent before operation, appear on the lateral and posterior walls of the pharynx. This condition is called "granular pharyngitis." It is easily seen on the posterior wall of the oral pharynx. Commonly when present in the oral pharynx, it is present in even greater amounts in the nasopharynx. When these follicles obstruct the internal ostia of the eustachian tubes, high tone impairment of hearing may result. Based on the work of Heinke[16] who in 1905 showed that lymphoid tissue is more susceptible to irradiation than the adjacent epithelium, muscle and bone, the hyperplastic lymphoid tissue was treated with roentgen rays or with radium with very excellent results in the most common type of impaired hearing.

Crowe found that more than 75% of children who had an adenotonsillectomy had postoperative marked recurrence of adenoid tissue in the nasopharynx, not because of poor surgery in the original operation but because of the tendency of lymphoid tissue to recur in the mucous membranes. This tissue cannot be entirely removed by any surgery because it is not practical to denude the nasopharynx of the mucous membrane. Repeated surgery is useless and radiation is the only satisfactory method of treatment. Even with radiation some recurrence of the lymphoid tissue may occasionally take place. I have the distinct impression that recurrence of lymphadenoid tissue occurs much more readily in the allergic than in the non-allergic child. I believe it is not too strong a statement to say that if a child has had an adenotonsillectomy by a competent surgeon and if eventually another operation is required because of regrowth to remove either the tonsils or adenoids, this is positive evidence in the author's experience that he is dealing with an allergic child.

About the first part of 1943 it was observed by Ward[17] working in Crowe's clinic that, among the hundreds of children being treated for prevention of deafness, there were a number with typical asthma. Many were sensitive to the usual inhalants but had failed to respond to hyposensitization and avoidance of dietary and environmental allergens. Nasopharyngoscopic examination revealed hypertrophied adenoids and lymphoid tissue scattered throughout the nasopharynx. In most of these children the attacks of asthma were preceded by coryza. Following radiation therapy the frequency and severity of attacks were in many cases reduced and in some instances the asthmatic attacks were even eliminated. This chance observation led to a careful nasopharyngoscopic study of a series of 34 patients, who had previously undergone adenotonsillectomy, with reference to the lymphatic tissue which had recurred in the nasopharynx after operation. These children were treated with exposure to radon gas on each side of the nasopharynx once

each month for an average of four treatments. In 23 of the 34 cases the lymphoid tissue completely disappeared. It was estimated that 68% of the children obtained from total to 50% relief while 32% obtained no relief.

The mechanism by which relief is obtained is not completely understood. Perhaps it is chiefly due to the elimination of foci of infection in the lymphatic follicles which act as a trigger mechanism. Other factors may be reduction of postnasal secretion; definite change in the bacterial flora and possibly a change in the threshold of absorption of allergens from the nasopharyngeal tissue after the lymphoid tissue has disappeared.

The indications as to the choice of X-ray or of radium for therapy do not appear as yet to be definitely established. Both act in an identical manner and so far as I have been able to determine, no permanent deleterious results have been reported in the literature from the use of either as yet. It would appear to me that the application of radium should be reserved for cases where the lymphoid tissue is limited in extent and well localized, as for example, in the internal ostium of a eustachian tube, and that X-rays would be indicated where the hyperplasia is diffuse. While Crowe and his associates prefer to use radium or radon in all instances, the literature indicates that the number of physicians favoring the roentgen ray is rapidly growing. If this proves to be as effective and as safe as radium or radon, there is little doubt but that it will replace the latter as the method of choice. The reasons are obvious. The employment of radon or radium may be a difficult technical procedure in small children, an anesthetic is sometimes required, and hospitalization is occasionally necessary. On the other hand, treatment by the roentgen ray is a painless office procedure of comparative ease, even in small children, and requires no intranasal manipulation. Roentgen therapy has been particularly advocated by Rosenblum, Pearlman and Uhlmann.[18]

Education

The training of the child for eventual self support must be considered in the case of the child with chronic asthma. But one study has been made of this subject. Flensborg[19] in Denmark investigated 298 asthmatic children and stated that 116 of these or about one-third had chosen a special profession on account of their asthma. It must always be borne in mind that once an individual suffers from asthma, even though a complete recovery may have been made, just as in the case of tuberculosis, there is always the possibility that a relapse may occur. This was well illustrated during the last war when many of my former child patients who had been discharged as "cured" again developed asthma when exposed to the rigors of military life.

There are certain occupations which are obviously unsuited for the asthmatic individual. These involve heavy manual labor, and other forms of excessive physical activity as professional athletics or the teaching of physical education; exposure to excessive dust, cold, moisture, strong odors, high or low temperatures and sudden changes in temperature. Bakers may develop asthma from exposure to flour dust; farmers as well as veterinarians and others exposed to animals are often sensitized to various epidermoids; beauty parlor operators are often sensitized to ingredients of cosmetics. It seems reasonable that asthmatic children should not, if they take up music, study wind instruments. The use of such instruments is difficult for dyspneic individuals and it is also probable that they increase the tendency to emphysema present in all asthmatics. It is of the utmost importance that the asthmatic child should be aided in the selection of a career in which, if asthma persists or recurs, the earning of a living will not be impossible.

Physiotherapy in Bronchial Asthma

The most common complication of long continued bronchial asthma is emphysema. In the adult this results in the typical picture of the "barrel shaped" chest with the shoulders elevated, the back hunched and the head thrust forward. Long continued bronchial asthma in the child produces a different type of deformity described in detail by Bock[20] and which, because of its resemblance in some respects to rickets he has termed "pseudo-rachitis asthmatica" or "asthmatic pseudorickets." The chief difference in appearance in true rickets and in this deformity is that while in true rickets the upper transverse diameter of the thorax is greatly narrowed, in asthmatic pseudorickets this diameter is greatly enlarged. This gives, roughly speaking, in both instances a pear-like appearance to the trunk. In asthmatic pseudo-rickets the larger portion of the pear corresponds to the upper thorax while in true rickets the pear appears inverted with the larger portion corresponding to the commonly distended abdomen below the flaring lower costal margins. In both instances the basic mechanism is the same, i.e. the effect of respiration under abnormal conditions. In rickets the primary factor is the softness of the thoracic cage responding to normal muscle pull; in asthmatic pseudo-rickets the primary factor is the abnormal muscle pull on a normally ossified thoracic cage.

Weiser[21,22] of Palestine has reported particularly brilliant results in the treatment of asthmatic children by physiotherapy. He states that the exercises employed are indicated in all cases of bronchial asthma showing a low vital capacity and cramped superficial breathing with poor chest expansion and little use of the diaphragm. Fisher in England[23] also reports good results from the use of exercises with less satisfactory progress in the "lung damage" type of asthma. Physiotherapy in this direction has been explored very little in this country and should be a fertile and productive field for investigation.

Psychosomatic Aspects

In asthma, as in any chronic disease, the psychosomatic aspects are of great importance and could very well have been discussed first rather than last in this presentation. This field has been recently briefly but well reviewed by Bakwin and Bakwin.[24] Some feel that psychologic factors are of primary importance in the etiology of asthma. Regarding this opinion it may be pointed out that the old saying that a chain is no stronger than its weakest link holds true here. Under stress and strain of psychic origin the weakest link will give way and in the case of an allergic child an allergic response may logically be expected. The child with asthma also will soon discover that he can use this as a defense in a difficult situation in the same way that any other child with any other illness may use that particular illness. In proportion as a child's asthma has failed to respond to the efforts of his physician so will a child feel less and less secure; a situation which becomes worsened if the parents, as is usually the case, show increasing evidence of anxiety as this state of affairs becomes increasingly manifest. That abnormal psychologic situations should occur under such circumstances is only to be expected. However, the best that can be hoped for from the psychosomatic approach is amelioration because no such approach can ever change the underlying allergic constitution. Every allergist has had the experience of seeing some new therapeutic advance relieve an occasional patient and under these circumstances the associated psychosomatic problems vanish like mist in the sun. In this connection one need only mention instances of urticaria of year's duration which have received adequate symptomatic relief from benadryl or pyribenzamine

resulting in an entirely new outlook on life on the part of these patients. Once we are able at will to relieve the allergic manifestations the associated psychologic problems will in most instances solve themselves although in a basically psychopathic individual the clinical manifestation of the abnormal state will, of course, express itself in some other form.

A primary consideration from the psychosomatic aspect in asthma, as in other chronic diseases, is the attempt to have the child lead as nearly a normal life as possible. The parents and other members of the household must control all expressions of anxiety, including those of excessive sympathy. It is also important to avoid any suggestion of rejection of the child however unintentional. Some member of the household must be thoroughly familiar with the symptomatic treatment of asthma, including the ability to skillfully administer a hypodermic injection of ephinephrine when necessary so that the child will have a feeling of security, knowing that he will not have to suffer unduly.

Besides being given a sense of security, the child must also be given some means of feeling a sense of importance or superiority in competition with those of his own age who are not afflicted with asthma. There are many methods of achieving this. If the child has the talent, he may be taught music or drawing or photography or to become a magician, etc. Collections of various types as stamps, coins, minerals, fossils, etc. are valuable as is also the building of models of airplanes and other objects. Care must be taken to avoid hobbies which have a distinct hazard from the viewpoint of allergy, as taxidermy, for example. My most conspicuous success with this form of therapy, although applicable to a child with asthma, did not occur in an asthmatic child. This was the case of a boy who was very small for his age but who had a burning desire to become a great athlete. His frustration resulted in a severe and almost fatal case of anorexia nervosa. Eventually he took up target practice with rifle and pistol. In this he was greatly helped by the cooperation of his father. The boy's desire for superiority was completely satisfied when he became a champion marksman who could hold his own regardless of the size of his competitors.

I also believe that it is now time, in order to help the asthmatic child have the feeling of living a relatively normal life, to establish camps for such children similar in principle to those which have been so useful in the case of diabetic children. If properly designed, located, and staffed, such camps could go far in enabling these children to lead more enjoyable lives.[25]

Conclusion

A very common error made in the treatment of the child with chronic asthma is failure to continue treatment after the child has been doing well for a period of weeks or months. Treatments should not be stopped until the child has been completely free from symptoms for a period of at least one year. If the child has been receiving injection treatments and is doing well, the intervals between the treatments may commonly be increased by increments of one week until the injections are given every four weeks but the child should be symptom free for at least one year before the treatments are discontinued.

Finally, it must be stated that there is a fairly large group of children, as well as adults, who suffer severely from and are more or less totally incapacitated by bronchial asthma who cannot be satisfactorily relieved by the measures outlined in the foregoing discussion. These patients demand care and study beyond that which their physicians can give, even with the best hospital facilities. There are now in this country no institutions where an asthmatic cripple may go for care and study, regardless of ability to pay, with the

single exception of the National Home for Jewish Children in Denver.[26] The need for an organization to develop and support similar institutions available for everyone and to do for asthmatics what the National Foundation for Infantile Paralysis, for example, is doing for individuals with poliomyelitis, is acute. This has been realized for many years and to meet this need the American Allergy Foundation* was organized. Despite the fact that this Foundation was established only three years ago, it has been possible this year to give grants totalling $25,000 for various research projects in allergy. Ultimately it is hoped that the Foundation will be able to establish institutions in various parts of the country where the effect of climate and all other phases of the asthma problem may be thoroughly studied from all viewpoints.

Summary

The management of the child with chronic asthma is discussed. The importance of possible prophylactic measures is mentioned. Environmental control is emphasized with special reference to the avoidance of house dust, feathers, wool, animal pets and strong odors. Change of climate is not always successful and it is important to do all that one can to relieve the child in his own community before this is considered.

The asthmatic child must be protected against respiratory infections. The usual measures of prophylaxis in pediatric practice must not be omitted but are all the more urgently indicated in the case of asthmatic children.

Recurrent lymphadenoid tissue in the nasopharynx following adenotonsillectomy is discussed in its relationship to bronchial asthma.

The possible use of physiotherapeutic measures for the prevention of asthmatic chest deformities and for assisting in the relief of chronic bronchial asthma is mentioned.

Psychosomatic factors are important and consist chiefly in giving the child a sense of security by means of a thorough understanding by the parent of the symptomatic treatment of asthma; the avoidance of coddling or rejection of the child; and teaching the child to excel in some special field so as to experience a feeling of superiority in competition with non-asthmatic children.

The asthmatic child should be aided in the selection of a career in which, if asthma persists or recurs, the earning of a living will not be impossible.

It is pointed out that the nature of the asthmatic problem is such that special facilities should be made available for research in all phases of the problem.

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PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

NURSING OR NURSES?

A Chance for the Future

We doubt that there is a pediatrician in our country who can have failed to be concerned about the difficulty in securing nursing care today for its patients. Adequate care in hospitals, schools, homes, physicians' offices, industrial plants is frequently not available; and many new services cannot even be begun because of the general inability to secure nurses. These facts have been the subject of several detailed studies by the nursing profession in recent months. The one of greatest importance and interest probably is "Nursing for the Future" prepared by Dr. Esther Lucile Brown for the National Nursing Council and published by the Russell Sage Foundation. Dr. Brown is an anthropologist who has studied carefully two other professions—social work and the law.

Two years of study of services given by nurses and the education they receive throughout the United States, and the cooperation of over two thousand physicians, administrators, nurses, and lay persons gave Dr. Brown the background from which she has written a most challenging book—one which needs the careful consideration of all those who are interested in the improvement of health in this country.

The role of the nurse in modern society and the education she should have is studied in an objective manner. The complexity of the problem is emphasized. The need for different types of skills is recognized. The work usually performed by "the nurse" is analyzed somewhat in the manner found useful in England when the lack of manpower was a problem of primary concern to the war effort. The job to be done is "de-skilled," as the English put it, that is, analyzed to see what functions can be performed only by professionally skilled persons and what functions can be relegated to those less skilled. Dr. Brown shifts the emphasis from "nurses" to "nursing." She points out that "so long as attention is centered on the graduate nurse, no other avenue is open except that of the present frantic and probably futile effort to recruit more prospective R.N.'s. Even appreciably better educational preparation is likely to be denied them, so insistent will the demand for nursing service continue to be. Once emphasis is shifted to *nursing,* however, several roads seem to point to potentially larger supplies of service and to possibly increased efficiency both on the nonprofessional and the professional levels." Dr. Brown believes that a group of simpler functions in nursing can be performed by a "non-graduate" nursing service—as, indeed, many of them are today by practical nurses, orderlies, ward maids, attendants, volunteers and the like. But to make such a program successful Dr. Brown points out: "No system of training for practical nurses is likely to succeed unless the public that creates broad general policy and provides funds, educators who design and operate instructional programs, hospitals and agencies that provide clinical facilities, and nursing associations and state boards of control that set standards and influence recruiting are prepared to manifest an active interest in practical nursing far beyond any interest yet shown."

The role of the fully trained nurse, called the "professional nurse" is fully discussed and would be of considerable interest to physicians (see Chapters IV and VI). Such a nurse would be trained only in a school which is able to furnish a professional education comparable to the education given other professions. She would be a skilled technician, and act as a specialist in "clinical practice, supervision, administration, teaching, or scientific research and writing."

But obviously most nurses today fall between these two extremes. Their education has been hampered by poor teaching, inadequate clinical facilities, and by the necessity of providing service during the entire time they are being instructed in the so-called fine art of nursing. That these graduates cannot be ignored is clear. Thus, Dr. Brown advocates that for the present time a middle category be recognized. But the real solution lies, according to this report, in recognizing clearly that nursing "schools" must truly become educational institutions of higher learning and that

nursing as now conceived must be split into two components. A first step is to establish a list of accredited schools—schools that can meet really good standards. When physicians recall the great advances that came after Abraham Flexner goaded the medical profession into closing the poor medical school, they should welcome Dr. Brown's insistence that a more active program of doing away with the poor nursing school is essential.

An item of particular interest to pediatricians in this report is the finding that nurses-in-training today, even as physicians, receive little or no education in the care of well or sick children. In more than one thousand hospitals reporting, 37% had no pediatric patients and 67% indicated that pediatrics was their minimum service. Moreover, in the "home" hospital used by schools of nursing in 1946 there was "an extreme lack of clinical facilities." In 1946 the median home hospital had a daily average of 134 patients; one-fourth had 84 or fewer patients.

This is a courageous report but courage in looking at itself is a characteristic of the nursing profession. Two previous studies of the role of the nurse in American culture in 1923 and 1928 made recommendations that led to many improvements but some of the recommendations in this report have a familiar sound. They are not unlike those in the previous reports. With the added impetus of the "crisis" in nursing today, one hopes that not only the medical and nursing professions, but public and private agencies of all kinds, will give heed to Dr. Brown's recommendations and find a way to act upon them promptly.

* * *

Two resolutions of particular interest to pediatricians were passed by the American Public Health Association at its 76th annual meeting in Boston, November 8th to 12th. Both of these were introduced by the School Health Section and were approved by a vote of the entire Association. The first had to do with the current practice of allocating tax monies to schools on the basis of the average daily attendance of pupils. Inasmuch as in some instances undue pressure is put upon children to attend schools when they are ill, it was believed that some more satisfactory method of allocating tax monies to local communities should be found. The resolution called for joint study and action of the Chief State School Officers and the State Commissioners of Health. The second resolution had to do with the advisability of joint planning of school health programs on the part of health departments and departments of education. Both of these resolutions are similar to those approved by committees of the American Medical Association and the National Education Association.

Another resolution called attention to the study of nursing, "Nursing for the Future" prepared by Dr. Esther Lucile Brown, which is reviewed above.

NEWS AND ANNOUNCEMENTS

At the 39th Annual Meeting of the National Committee on Mental Hygiene in New York recently, Dr. C. Anderson Aldrich, Director of the Rochester Child Health Institute, Mayo Clinic, was presented the $1,000 Lasker Award for 1948.

Dr. George Baehr, president of the New York Academy of Medicine, presented the award to Dr. Aldrich for "outstanding accomplishment in education of the physician in the psychologic aspects of the practice of medicine." Community responsibility for the improvement of mental health of the nation was the point of emphasis at the meeting, and Dr. Baehr described the field of pediatrics as "the most forward looking branch of medicine, one which has assumed its share of preventive psychiatry as no other branch of medicine has done."

* * *

Retirement of Dr. Stanley Gibson as Chief of Staff of The Children's Memorial Hospital, Chicago, Ill., has been announced. Dr. Gibson, who has been on the staff since 1932 and chief of staff since 1944, will continue to serve as consulting cardiologist.

Dr. John A. Bigler has been appointed to succeed Dr. Gibson. Dr. Bigler has been a member of the hospital's medical staff since 1931 and Assistant Physician in Chief and Medical Director since 1944.

* * *

The Maurice Lamm Blatt Memorial Fund announces a prize of $250.00 to be given for a piece of original research work done by an intern or resident of the Cook County Hospital or a former intern or resident who has been out of the hospital for a period of not more than five years. All communications should be addressed to the Maurice Lamm Blatt Memorial Fund Children's Division, Cook County Hospital.

* * *

The American Heart Association announces that fellowships for research in cardiovascular disease are available. Application blanks may be obtained by writing: Medical Director, American Heart Association, 1775 Broadway, New York 19, N.Y.

The recommendations of the Research Policy Committee were published in the *American Heart Journal* **36**:463, Sept., 1948. The policies are subject to modification by the membership of the Scientific Council of the Association and approval by the Board of Directors.

The AHA research program, which has as its aim the development of a continuing program of productive research within the broad field of diseases of the heart and blood vessels, will be coordinated closely with that of the National Heart Institute of the National Institutes of Health, U. S. Public Health Service and with the Life Insurance Medical Research Fund.

* * *

The National Foundation for Infantile Paralysis announces the availability of fellowships in Research, Physical Medicine and Public Health.

Research fellowships are available in virology, orthopedic surgery, pediatrics, epidemiology and neurology. They are intended to emphasize (1) advanced training in the basic sciences as they apply to the particular specialty and to research, and (2) experience in research, which need not be immediately related to poliomyelitis.

Clinical fellowships in Physical Medicine are available to physicians who wish to prepare for eligibility for certification by the American Board of Physical Medicine.

Postgraduate Public Health Fellowships are available to physicians for one year of postgraduate study leading to a Master of Public Health degree at a school of public health approved by the American Public Health Association.

For eligibility requirements and applications write: National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N.Y.

* * *

The Northwestern Pediatrics Society announces the election of the following new officers: Dr. L. G. Pray, Fargo Clinic, Fargo, N.D., President; Dr. Northrop Beach, Nicollet Clinic, Minneapolis, Minn., Vice-President; and Dr. Elizabeth C. Lowry, 301 Kenwood Pkwy., Minneapolis, Minn., Secretary-Treasurer.

Dr. Joseph Stokes, Jr. will deliver the seventeenth annual series of the Benjamin Knox Rachford Lectureships February 1 and 2, 1949, at 8:30 p.m. in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati, Ohio. The general title of his lectures will be "Viral Hepatitis."

* * *

A postgraduate refresher course for qualified pediatricians will be held February 7 to 12 at Tulane University School of Medicine in New Orleans. For particulars, write to Dr. William Frye, Director of Postgraduate Medical Education, or Dr. R. V. Platou, Head of the Department of Pediatrics.

* * *

The University of Minnesota announces a continuation course in pediatrics to be given at the Center For Continuation Study on February 7, 8, and 9, 1949. The course is intended for general physicians and will be concerned chiefly with problems of the premature and newborn infant.

* * *

The Harvard Medical School announces a two weeks' intensive course in graduate pediatrics by the Children's Medical Service, Massachussetts General Hospital, June 13 to June 25, 1949, 9:00 A.M. to 4:30 P.M. daily. Recent advances in pediatrics will be emphasized. For details write Courses for Graduates, Harvard Medical School.

* * *

The following candidates were certified by the American Board of Pediatrics following examinations in Atlantic City, N.J., on November 17, 18, and 19, 1948:

Frederick Merrill Adams, 322 Wabeck Building, Birmingham, Mich.
Reginald Anthony Allen, 233 Thayer St., Providence, R.I.
William Dewey Alsever, 836 Lancaster Ave., Syracuse 10, N.Y.
Grace A. Altenau, 725 4th Ave., Brooklyn 32, N.Y.
Perry P. Amick, 310 Bankers Trust Building, Des Moines, Iowa
Oscar Randolph Batson, Vanderbilt University Hospital, Nashville 4, Tenn.
Nina Bleiberg, 4153 49th St., Long Island City 4, N.Y.
Irving Frederick Burton, 14608 Gratiot Ave., Detroit, Mich.
Maclyn Cagan, 60 Ridge Rd., North Arlington, N.J.
Vincent P. Casey, 3105 Roberts Ave., New York, N.Y.
Walter L. Cohn, 511 Cottman St., Philadelphia 11, Pa.
Edward Perry Crump, Meharry Medical College, Nashville, Tenn.
William Anderson Dickson, 266 Beacon St., Boston, Mass.
Benjamin Dickstein, 6725 Castor Ave., Philadelphia 24, Pa.
Edward C. Dyer, 330 Dartmouth St., Boston 16, Mass.
Jane A. Erganian, 122 Rodney St., Glen Rock, N.J.
Katherine W. Evans, 8236 Germantown Ave., Philadelphia 18, Pa.
Mervin Edward Fischman, 264 Clinton Pl., Newark, N.J.
William C. Friedman, Glenwood Terrace Apts., 1409 Greenport Rd., Far Rockaway, N.Y.
Margaret Eugenia Geib, 1277 Clinton Pl., Elizabeth, N.J.
Elizabeth Alice Gregory, 255 Massachusetts Ave., Arlington, Mass.
Howard Yeager Harris, 40 James St., Kingston, Pa.
Ruth Cameron Harris, Babies' Hospital, 3975 Broadway, New York, N.Y.
Andrew Dickson Hunt, Jr., Children's Hospital, 1740 Bainbridge St., Philadelphia 46, Pa.
Mary Elizabeth Hyman, 45 East 82nd St., New York 25, N.Y.
J. Hoyt Kerley, 167 E. 82nd St., New York 28, N.Y.
Josephine Gross Kety, Children's Hospital, 1740 Bainbridge St., Philadelphia 46, Pa.
Harold Klein, 522 Eastern Pkwy., Brooklyn, N.Y.
Joseph C. Knox, 15 N. 5th St., Wilmington, N.C.
Louis L. Krafchik, 158 Livingston Ave., New Brunswick, N.J.
Saul Krugman, Children's Medical Service, Bellevue Hospital, New York 16, N.Y.
Martha Frances Leonard, 55 N. 5th Ave., Highland Park, N.J.
Warren D. Leslie, Riley Law Bldg., Room 400, Wheeling, W.Va.
Ann Lublin, 18472 Whitcomb St., Detroit 19, Mich.

Donald Fraser Lyle, 5711 Thomas Ave., Philadelphia 43, Pa.
Lillian Marks, 1270 Bryden Rd., Columbus, Ohio
Clarice L. McDougall, 616 Medical Arts Bldg., Grand Rapids, Mich.
John D. McKey, 320 N. Main, Orlando, Fla.
Henry Mitchell Putnam, 743 High St., Dedham, Mass.
Arthur Robinson, 908 Magnolia St., Denver 7, Colo.
James Harold Root, Jr., 103 N. Main St., Waterbury, Conn.
Jonas Samuel Rosenberg, 219 Washington Ave., Batavia, N.Y.
Maurice Ross, 372 Maine St., Saco, Me.
Estelle Siker, 301 Westchester Ave., Port Chester, N.Y.
Arthur I. Sims, 3215 Columbia Pike, Arlington, Va.
Alex J. Steigman, Children's Hospital, Elland & Bethesda, Cincinnati 29, Ohio
Edward Hoge Vick, 323 N. Narberth Ave., Narberth, Pa.
Betty Willis Whitehead, Chatham, Va.
Milton Michael Willner, 822 S. 12th St., Newark, N.J.
Natalie Yarow, 1215 Fifth Ave., New York, N.Y.
Alex C. Zarchy, 593 Central Ave., Cedarhurst, N.Y.

Future examinations are scheduled for February 18, 19 and 20 in St. Louis, Mo., and May 7, 8, and 9, 1949, in Baltimore, Md.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

When the new building at the Hospital for Sick Children, Great Ormond St., London, was opened in 1938, a special unit was set apart for babies with gastro-enteritis and much interesting research work has been carried on in this department. After the disorganization of the war period, the unit came into operation again and early in 1946 the Medical Research Council financed a whole-time bacteriologist and also an epidemiologist based at the hospital, but available for investigating outbreaks in other institutions. Visits of this small team, who often arranged to bring back a sample baby or so, indicated that in many instances institutions were not favourably equipped with staff or apparatus for dealing with an outbreak.

In consequence, The Hospital for Sick Children has now organized a flying-squad to go to the help of institutions or others in difficulties over an outbreak of infantile gastro-enteritis. The scheme has the blessing of the Ministry of Health and is partly financed by the King Edward's Hospital Fund for London. One medical officer has been appointed for the team, which also includes five fully trained nurses. All these will also work in the unit at Great Ormond St., when not out at an emergency. Equipment will be taken in a lorry which, besides taking every requirement for transfusions of fluids, including blood, will also carry apparatus for bacteriologic studies. In this way, the flying-squad will supplement the work of the research team and it will be interesting to see the sort of experience obtained in the coming months.

BOOK REVIEWS

MENTAL HEALTH IN MODERN SOCIETY, Thomas A. C. Rennie, M.D., and Luther E. Woodward, Ph.D. 424 pages, $4.00. The Commonwealth Fund, New York, 1948.

As another evidence of the emergence of psychiatry from the hospital and the new concept of its role in society, this book offers an excellent integration of mental health theory and practices in their relation to a multitude of social problems. Prompted, apparently, by the advances of psychiatry during the war period and including a thorough study of the mental health problems of the veteran, this book is a compendium of modern resources in the field with some thoughts on the varying usefulness of their application.

The first part deals with the lessons of the war itself and contains, in addition to a chapter on the psychiatric services in the armed forces and the emergency measure for dealing with the veteran, an excellent chapter on "The Psychiatric Disabilities of War: Dynamics and Motivation." It is obvious in reading this chapter that the application of this knowledge is quite universal and the presentation of these dynamics is unusually clear.

A summary of "Continuing Mental Health Problems and Needs" comprises the second section of the book and leads the way to the third part where the sources of help in treatment and prevention are discussed. This last section not only explains the role of the various professions which are involved in mental health procedures: the physician, the social worker, and the psychologist, but interrelates their work with that of the pastor and with the plant physician as well as the "boss" in industry. The dynamic knowledge of the authors makes it possible for them to point out the difficulties encountered in mental health work by untrained people while stressing the very positive opportunities for doing good work that are available to the minister and the foreman. Throughout its discussion of resources for the patient the book does not minimize real problems but presents the working conclusion that division of labors can be a real help in solving these problems. The helpfulness of the book is also enhanced by the extensiveness of the bibliography at the end of each chapter and by the orderly progression of chapter material.

Of special interest to those dealing with children is Chapter XII on "The Mental Hygiene of Family Living." Here is recapitulated the basic framework of security on an emotional basis with the most current conceptions of this basis from the knowledge of psychiatry. This chapter points the way to the making of the mature individual and is followed by a chapter on education which carries the progress of this idea further. This logically leads into the final chapter where Chisholm's idea of the mature individual in his total social relations is expounded. This chapter contains the philosophic aspects of the book outlining the relation of mental health to the health of society and, accordingly, the varying responsibility of medical and social scientists.

HENRY H. WORK

THE CARE AND FEEDING OF PARENTS, William Hall, $2.00, 117 pages, with illustrations. Thomas Y. Crowell Co., New York, N.Y., 1948.

A layman speaks the truth and a sound philosophy about what small children think and reason about this world. The author uses as sources of material his own three children and follows in general the style of "Infant Care," a booklet "credited to the Department of Labor." There is a great deal of humor on the surface and many illustrations in line drawings add greatly to this phase of the book. There are many short chapters on special subjects on child care and psychology. Underneath the fun and frolic of the book, which can best be realized by parents who have passed "through it all," is a sound presentation of viewpoints for parents who are still in the process of raising small children. If such parents could drop out of character long enough to pick up a little perspective, the book should make life easier for them and should help them to enjoy their children more. The author's style on the whole is on the humorous side, but he is to be congratulated on the story he unfolds. Even though he is a layman, he has followed a professional presentation. Pediatricians will be highly amused, entertained, and not a few will find good solid "meat."

HUGH MCCULLOCH

ADVANCES IN PEDIATRICS, Vol. III, S. Z. Levine, Allan M. Butler, L. Emmett Holt, Jr., and A. Ashley Weech. 363 pages, with illustrations. Interscience Publishers, Inc., New York 3, 1948.

An annual presentation of selected subjects in the nature of a review assigned to individual authors, recognized in that field of study. As stated in the preface, three of the eight subjects indicate the shift in pediatric thinking to the protection of promotion of health, especially in the field of psychologic and social adjustment. The following is a list of authors and subjects:

Effects of Birth Processes and Obstetric Procedures upon the Newborn Infant, Clement A. Smith.
Retrolental Fibroplasia, T. L. Terry.
Emotions and Symptoms in Pediatric Practice, Milton J. E. Senn.
Therapeutic Agents in the Treatment of Epileptiform Seizures, William G. Lennox.
Viral Hepatitis, Joseph Stokes, Jr.
Abnormalities and Variations of Sexual Development during Childhood and Adolescence, Lawson Wilkins.
Puberty and Adolescence: Psychologic Considerations, Hilde Bruch.
The Osteochondroses, Beckett Howorth.

BABY CARE FROM BIRTH TO BIRTHDAY, Edmund G. Lawler, M.D. $3.95. 366 pages, 218 illustrations. Wilcox and Follett Co., Chicago 5, 1948.

The book is well printed and beautifully illustrated. It takes a middle ground in respect to matters of infant care, particularly those of a controversial nature.

GROVER F. POWERS

JUNIOR SPEAKS UP, Irving R. Abrams, $2.50, 164 pages. MacMillan Co., New York, N.Y. 1948.

Noteworthy for its style of presentation in the form of characters, speaking somewhat as those in an Elizabethan play or movie. Terse, crisp, pungent erudite discussions in dialogue of common problems concerning a growing child. The author is to be congratulated on the introduction of "Shadow" a character foil for "Junior" to reason out his own thinking and approach to these problems. It is here that the author shows his skill in opening up a child's mental processes and probable reactions, reflexes and response to the many environmental influences that are thrown, thrust and imposed on him. The text is easy to read, and the book is delightful, suitable for selected parents. In an appendix, the author drops back to a conventional presentation of ordinary directions for child health and care.

HUGH MCCULLOCH

DEVELOPING YOUR CHILD'S PERSONALITY, Gelolo McHugh, Ph.D., $2.75. 234 pages, D. Appleton-Century Co., New York 1, 1948.

An attractive, easy to read presentation of the important principles which the intelligent and information-seeking parent may ask about help. The level of thinking involved in the presentation of information, however, restricts the parents who can follow it to those who need the book the least. The book will be useful to teachers and students in training in child psychology. The pediatrician will also find it most useful because of its clearness, brevity and straight to the point manner in the presentation of ideas. He will alsp find that the psychologist is the person to deal with these problems as a specialist. The information and method of presentation of ideas is according to the best practices in pediatrics.

HUGH MCCULLOCH

Pediatrics

VOLUME 3 JANUARY 1949 NUMBER 1

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

REPORT OF THE SECRETARY

This has been a year of meetings. We have already had Areal Meetings in Buffalo, Milwaukee and Seattle, and now comes the Annual Meeting. For the year 1949, we plan to have but two meetings: the Areal Meeting at Atlanta, Ga., April 13-15, and the Annual Meeting at San Francisco, Calif., November 14-17. There are two reasons why the number of meetings has been reduced. The first is that the force in the central office is too overloaded with work to carry on four meetings a year. The second, and all important, is that the commercial firms will not support so many meetings in one society. As a consequence, we stand likely to have a deficit in each of the three areal meetings. However, in two of these, one of the commercial firms assured us that it would make up any deficit, so that we are now in a position to write these two meetings off the books. I wish to call your attention to the meeting of the Second Pan-American Congress of Pediatrics at Mexico City from November 2-5, 1949, which will be under the direction of the Mexican pediatric group.

Very few of our members have any conception of the amount of work which must precede one of our meetings, nor have they any conception of the amount of routine work which must be done in the central office. It seems likely that, in the not too distant future, we must enlarge our quarters and employ more help.

One of the most encouraging things that has happened in the last year has been the way the committees have taken hold of their jobs and carried them out. Of the Standing Committees, the Committee on School Health has been so regularly efficient that it becomes routine for us to exclaim about it. Such Committees as the Committee on Fetus and Newborn have done outstanding work. The Committee on Legislation has been on the job regularly. The Committee on Governmental and Medical Agencies has been discharged with thanks and its work is taken over by the Committee for Improvement of Child Health. This last committee, under the direction of Dr. James L. Wilson, and with an efficient secretary in the form of Dr. Hubbard, is rounding into form and will have many suggestions to make to the Academy. It is interesting to note that they have been able to raise all but about $5,000 of their $75,000 budget and that $5,000 is now promised. The Committee on Medical Education is working in close cooperation with the Committee for Improvement of Child Health. The Committee on Mental Health is reorganizing. The Committee on Pan-American Scholarships, whose work has been in abeyance for several years, will probably renew its efforts in the near future. The Committee on Cooperation with Non-Medical Groups is developing its program, which is a rather difficult one to carry out because of the many organizations to take into consideration.

Of the other Standing Committees, the Committee on Pediatric Awards has done its usual job and done it well; and the Program Committee, under the direction of Dr. Edgar Martmer, has been working hard and efficiently.

Presented to the Executive Board at the Annual Meeting of the Academy, Atlantic City, N.J., November 20-23, 1948.

When we come to the Special Committees, several of these stand out in importance; the Committee on Mothers' Milk Bureaus, the Committee on Rheumatic Fever and the Committee on Care of European Children. The Budget Committee has instituted a new era in the finances of the Academy. The Committee on Reorganization is working hard and will have some excellent propositions to present. The Committee on Post-War Courses in Pediatrics has been discharged with thanks and the Committee on Child Health Services will have completed its survey and be dismissed by the first of the year. The Tumor Registry Committee is doing an excellent job and Dr. Dargeon has associates with him, many not in the Academy, who will help in perfecting the recommendations of this committee. One thing is very apparent and that is, that if we wish the most efficient committees, we must make some arrangements for meetings at relatively short intervals. It is not sufficient that these committees should meet only at the time of the Annual Meeting. There should be some provision made whereby the committees could meet at least once during the intervals between Annual Meetings, preferably, according to the opinion of the Secretary, just before the June meeting of the Executive Board. With the committees as now constituted, this would be a heavy financial burden, but if the number of members in each committee were reduced to five, including the Chairman, and if only those committees having active programs were granted the right to have such a meeting, it might be possible to finance such meetings.

Of increasing importance to the Academy is the work of the Liaison Officers. These men have more and more tied up the work of the Academy with allied organizations and made it possible to cooperate effectually with them.

Certainly the Secretary should not conclude his report without calling to the attention of the Executive Board and the members the excellent job which has been done by the Editor of PEDIATRICS and his Editorial Board and the careful attention to details, principally of finances, which has been the work of the Publication Committee. We may all be thankful for the efficiency of both these groups and we may look with confidence to the future of the publication which now belongs to the Academy.

With the rapid growth of the Academy, changes must come and it is significant and important, that these changes should come from the body of the membership. With the activity of Dr. Baty's committee, I feel assured that these changes will be very definitely for the benefit of the Academy. These will, largely, turn to the question of more democratic procedures in the organization. This, in turn, means a greater interest on the part of the members.

It is now my sad duty to list the deaths which have occurred since my last report to you:

Dr. John Aikman, Rochester, N.Y.
Dr. Walter C. Bacon, Baltimore, Md.
Dr. Bert I. Beverly, Oak Park, Ill.
Dr. Alberto C. Gambirassi, Buenos Aires, Argentina
Dr. Lawrence E. Goldman, Clayton, Mo.
Dr. George Clifford King, Fall River, Mass.
Dr. Abel Lax, Outremont, Quebec, Canada.

Respectfully submitted,

CLIFFORD G. GRULEE, M.D., *Secretary*

REPORT OF THE TREASURER

STATEMENT OF RECEIPTS AND DISBURSEMENTS
JULY 1, 1948 TO OCTOBER 30, 1948

Balance in checking a/c—July 1, 1948		$ 18,974.49
Balance in savings a/c—State Bank & Trust Co.		15,708.99
Balance in savings a/c—First National Bank & Trust Co.		9,176.50
		43,859.98
Receipts:		
Dues	$60,294.50	
Exhibits—Milwaukee, Wis., June, 1948	100.00	
Seattle, Wash., Sept., 1948	1,887.50	
Atlantic City, N.J., Nov., 1948	10,727.50	
Areal Meeting—Milwaukee—Registration	1,018.75	
Seattle—Registration	735.00	
Seattle—Cash taken in	1,400.00	
Annual Meeting—Atlantic City, N.J.—Seminars	6,125.00	
Registration	7,509.50	
Round tables	2,822.00	
Initiation Fees	2,850.00	
Interest Earned	327.50	
Pamphlets—Child Health Record $ 223.50		
Immunization Procedures 125.07	348.57	
Committee—Improvement of Child Health	40,255.00	
International Congress Assessment	50.00	
PEDIATRICS	21,010.00	157,460.82
		$201,320.80
Disbursements		
Annual Meeting—Dallas, Dec. 1947	175.50	
Atlantic City, Nov. 1948	1,501.86	
Areal Meeting—Buffalo, April, 1948	151.40	
Milwaukee, June, 1948	2,672.52	
Seattle, Sept. 1948	3,911.57	
Bank Charge and Exchange	45.06	
Certificate Expense	97.63	
Executive Board	2,583.62	
Meetings—General	12.25	
Miscellaneous	255.01	
Office Supplies & Equipment	124.57	
PEDIATRICS	19,150.00	
Postage	152,75	
Rent	906.10	
Salaries—Secretary $ 6,000.00		
Ass't Secretary 1,666.66		
Office 3,536.61	11,203.27	

Stationery & Printing		301.10	
Telephone		202.72	
Travel Secretary		622.89	
Treasurers' Bonds		82.50	
Expense—Districts	54.20		
States	19.61		
Committees	22,950.04	23,023.85	
Pamphlets—Child Health Record	23.89		
Immunization Procedures	7.45	31.34	
Refund to Mead Johnson & Co. for unused portion of sum allotted for Post War Courses		4,345.40	71,552.91
Balance—October 30, 1948			$129,767.89
Balance in checking a/c—October 30, 1948			102,032.40
Balance in savings a/c—State Bank & Trust Company			18,558.99
Balance in savings a/c—First National Bank & Trust Co.			9,176.50
			$129,767.89

REPORT TO EXECUTIVE BOARD FROM THE COMMITTEE FOR IMPROVEMENT OF CHILD HEALTH

The findings of the Study of Child Health Service clearly indicate the need for (1) the strengthening of pediatric training in medical schools so that all doctors, not only specialists, may be thoroughly prepared to care for children and (2) the development of systems of decentralized training and rural extension services so that better medical care may be available in outlying areas. The Committee proposes:

1. The visit pediatric departments and arrange meetings of pediatric educators in order to provide opportunity for discussion of the information collected during the Study in relation to content, curriculum and technics of teaching.

2. To Study and evaluate decentralized systems of pediatric education and hospital services. Rotation of hospital residents, fellows or other physicians-in-training through periods of service in outlying community hospitals affiliated with the teaching center, brings the skills and services of medical centers to the very areas where deficiencies in medical care have been shown to exist. Such decentralization of teaching and service also helps the general practitioner in rural areas to keep abreast of the new advances in medicine. A compilation of the experiences of systems already in operation should prove a valuable guide for definitive planning and not only raise the standards of pediatric education but also bring immediate improvement of care to children.

3. To keep a current roster of approved pediatric residencies and postgraduate courses.

4. To make available to the AMA the findings of the study and, without prejudice to the justification of federal grants for pediatric education, hold in abeyance action to seek federal aid pending current action of the AMA to raise necessary funds from other sources.

5. To continue the collection and analysis of data and assist state chairmen in the completion of their reports and the development of state programs for the improvement of child health.

6. To assist the Rheumatic Fever Committee to evaluate state and local rheumatic fever programs.

7. To recommend a committee to promote pediatric nursing education.

8. To provide suitable publicity toward informing the profession and the public of the opportunities for better health for all children that lie in the strengthening of pediatric education and programs of decentralization of teaching and services.

Approximately two thirds of our annual operating budget will be spent toward the items concerned with pediatric education and the other third is earmarked for the continuance of analysis and aid to state programs. These funds have been raised from foundations and commercial houses for the first year. Academy fellows have made voluntary contributions totalling more than $2,000.

* * * *

It is understood by your Committee for Improvement of Child Health that one of its primary purposes is to study the report of the Committee for the Study of Child Health Services and to submit to you recommendations for action based upon the factual information contained therein.

At the beginning, the Committee would like to emphasize that it is well aware of the great progress which has been made in the medical care of children in America in the last half century. The medical profession can be proud of this record. Our deep concern has been to analyze the progress which has been made. Only with such a background can we determine the different emphases which will and can result in better care to more children. How can our present system of medicine operating in the framework of private practice be improved?

The Committee would further call to your attention that there are many groups in the country pursuing similar objectives to our own. For instance, the A.M.A. has an extensive program underway under the direction of its Committee on Rural Medical Service. The Hospital Survey and Construction Act is recognition of the need for increased hospital facilities in rural areas. The Saltonstall

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Prepared at a meeting of the ICH Committee in New York, September 27 and 28, 1948. Approved by the Executive Board subject to certain revisions which have been made in this final draft.

Bill (S. 2189) which proposes federal aid in the establishment and maintenance of local health units throughout the United States has the backing and approval of the A.M.A. Many medical schools and hospitals are showing an increasing awareness of their responsibility for improving the supply and training of physicians in rural areas.

Through its impressive and unprecedented nation-wide study the American Academy of Pediatrics is now in a position to lend the full weight of its powerful organization to the development of an action program based upon the information it has collected. Ever since its foundation one of the guiding principles of the Academy has been that it should provide leadership in all movements designed to improve child health. Never has it been faced with a greater opportunity or a greater responsibility to provide that leadership than at present.

Review of National Report

Each member of this Committee has given careful and critical attention to a draft of the report under the title of Health Services for Children and Pediatric Education in the United States. The following important findings of the Study—some of which were already known in general terms but have now been described precisely—stand out as highlights from which action programs may profitably be developed:

Findings Related to Pediatric Education:

1. The Committee feels that the problems related to pediatric education warrant first attention. The survey shows that the present system of medical education is not well adapted to training physicians for general practice, one-third of which is concerned with the care of children. Although certain schools provide over 300 hours of clinical training in pediatrics, the average is 161. In one school students are graduated having received only 28 hours of actual contact with child patients.

2. The ability of a physician to treat children cannot be fully measured by his pediatric hospital training. Nevertheless such training is clearly of great importance as a background for the practice of modern medicine. Only about two out of five physicians now graduating from medical school receive pediatric intern training in hospitals approved for pediatric residency training; two-thirds of this number serve for six weeks or less. Small wonder than that 45 per cent of the general practitioners report less than one month of hospital training in pediatrics.

3. Whereas about one-third of the general practitioner's care of children and over half of the pediatrician's practice is devoted to health supervision of well children, comparatively little attention is given by formal exercises in the medical school or teaching hospital to the preventive aspects of child care or normal growth and development.

4. Attention should be directed to the crisis now confronting medical schools as a result of inadequate financial support. Pediatric departments are especially handicapped. Half of the medical schools have pediatric budgets less than $25,000; 21 departments have budgets less than $10,000 and 11 less than $5,000 annually.

5. A large part of pediatric teaching is done by pediatricians who depend on their private practice for a livelihood and receive little or no remuneration for their time given to teaching or service to hospital clinics. Pediatric members of hospital staffs who give less than one-quarter of their time to teaching comprise over half of the entire teaching staff and, as a group, account for nearly one-third of the aggregate teaching hours.

Findings Related to Services:

1. The distribution of medical care for children has been presented in specific detail. Children in or near cities receive 50 per cent more care than those in isolated counties of the United States. One state has five times as many physicians as another in relation to child population; some states provide over three times as much hospital care for children as others. At the same time, it must be recognized that the Study has not provided data on the unequal distribution of medical care within cities or urban areas, nor does it have information on other important factors related to health such as levels of nutrition, general sanitation, climatic influence on disease, etc.

2. Pediatricians are for the most part available only to children in or near cities. Three-quarters of the nation's practicing pediatricians are in cities of 50,000 or more population, one-half in the relatively few counties classified as greater metropolitan. Pediatricians however are increasing rapidly

in number and distribution and are now making one out of every eight visits to children. But it is a fact that three-fourths of the private care of children is in the hands of the general practitioner. Not only do general practitioners take care of most of the sick children, but also they, as a group, do most of the well child supervision.

3. The amount and quality of hospital care available to children are comparatively low in isolated counties and in the south; out-patient services are almost non-existent outside of the metropolitan counties. The survey has no data on the actual demand for more pediatric hospital facilities in isolated areas in comparison with urban areas. This point merits further study in view of current planning under the Hospital Survey and Construction Act.

4. Community health services, such as well child conferences, are sparse in some states and are to be found predominantly in metropolitan counties. Public or privately organized health services for children do not fill the gaps left by private practice. There is need for further study of the adequacy of local health units in relation to child health.

Proposed Action

Facts such as the above can be used by many different agencies and organizations to support widely varying policies and programs. Many groups, both state and voluntary, are waiting for results of the Study for their own guidance.* These findings are already becoming public property from their release in state reports. Prompt action is therefore indicated in the development of the Academy's own projects.

This Committee is convinced that the first and most definitive project directed toward the improvement of child health must be centered in an effort to provide more physicians who are well trained in the care of children, especially in the remote and rural areas where the greatest deficiencies have been shown to exist. It is clear that this need must be met before other health measures can be effected.

Improvement of Pediatric Teaching in Medical Schools:

On many occasions during the course of the Study of Pediatric Education, the Committee was asked to advise on content, curriculum and techniques of teaching with specific reference to the findings of the Study. Many department heads requested further conferences of pediatric educators to provide opportunity for exchange of opinion in regard to pediatric education.

The Academy Committee on Education, as a result of their experience during the survey, has requested assistance from the ICH Committee in this regard. It is, therefore, proposed that the ICH Committee, through its Executive Staff, undertake to organize meetings of pediatric educators. It is proposed also that the Executive Director visit schools in order to discuss with the heads of pediatric departments information collected during the survey, much of which could not be condensed in the report.

Planning for Extension of Pediatric Teaching and Service:

It is the opinion of this Committee that it is of paramount importance to stimulate the development of decentralized systems of pediatric teaching whereby hospital residents, fellows, or other physicians-in-training, rotate through periods of service in outlying community hospitals affiliated with the teaching centers. The skills and services of the teaching centers may thereby be extended from the medical centers to the very areas where deficiencies in medical care have been shown to exist. This decentralization of medical education and services will help general practitioners in outlying or rural areas to keep abreast of the latest developments in the teaching centers much more effectively than the present method of encouraging general practitioners to attend infrequent postgraduate seminars or lectures at medical centers. In brief, this plan will not only raise the standards

* The Committee on Maternal and Child Health of the State and Territorial Health Officers' Association, at a meeting held in Washington, November 1948, took the following action: "It is recommended that the findings of the study on child health of the American Academy of Pediatrics be widely used as reference material in planning Maternal and Child Health Programs and be used as a vehicle for close relationship between practicing physicians and health departments in their joint endeavors to improve child health."

of pediatric education but will bring immediate improvement of care to the child population of the country.

As a first step toward this objective, your Committee proposes through its Executive Director, to study and evaluate those systems and centers already in operation or planned in which medical teaching and service is extended to outlying areas in the same state or neighboring states. Many centers throughout the United States have already gained valuable experience along these lines. The Bingham Associates' extension services from Boston throughout Maine is perhaps the foremost. Other plans, more specifically pediatric, are operating or developing under the aegis of the pediatric departments of Tulane University, and the Universities of Michigan, Illinois and Rochester. A compilation of the experiences, successes and failures of such centers should prove a valuable guide for the development of other centers elsewhere.

Roster of Facilities for Graduate and Postgraduate Training in Pediatrics:

The demand for pediatric residencies and postgraduate courses has become so great that the Committee feels it can offer valuable service by maintaining an up-to-date roster of all currently approved residencies and postgraduate courses in pediatrics. Such a roster should facilitate the filling of vacancies and aid in the further development of pediatric residencies and postgraduate courses.

Present Status of Recommendation for Federal Support of Pediatric Education:

Subsequent to this Committee's recommendation for federal support of pediatric education, approved by the Executive Board on February 8 and again on April 30, 1948, the AMA has initiated plans to attempt to raise from private sources a large fund annually for medical education. Consequently on June 26, 1948 the ICH Committee recommended to the Executive Board that action to seek federal aid be held in abeyance without prejudice to justification of federal aid or its need. This recommendation was approved. The Committee also recommended that this plan of the American Medical Association to raise funds for medical education be supported by the Academy.

Upon several occasions the Academy's Study of Pediatric Education has been brought to the attention of both the AMA and the Association of American Medical Colleges. It is now recommended that the findings of the Study be made available to those organizations with particular reference to their forthcoming general survey of medical education.

Nursing Education:

The ICH Committee recommends that the Executive Board appoint an Academy Committee on Pediatric Nursing Education to meet with groups of nurses concerned with nursing education. Owing to the many overlapping aspects of medicine and nursing education in pediatrics, it is suggested that one or more members of the Academy's Committee on Education be included.

Consultant Services for State Reports and State Programs:

Of immediate concern not only to state chairmen but to the agencies which participated in the state studies, is the early completion of state reports and recommendations. So important are these reports regarded by public and private agencies that some are holding in abeyance their own planning until the Academy's findings in their respective states are available. With the completed state data in the hands of all state chairmen since last June, cooperative planning can be done with state medical organizations toward the blending together of pediatric service and training with medicine in general.

To date, several state reports have been completed. Almost daily requests are received from state chairmen for consultation and advice related to the interpretation of state data. It has already been set forth as a responsibility of the ICH Committee to assist state chairmen in the completion of their reports and in developing state programs based on the findings. To meet the requirements of state chairmen, Mrs. Maryland Y. Pennell, statistician and health economist of the U. S. Public Health Service who has been with the Study since its beginning, continues on the staff of the ICH Committee. Office space for Mrs. Pennell and several statistical assistants has also been provided by the Public Health Service in Washington. This important function of the Committee will undoubtedly be required until the last state report is completed and is expected to consume about one-third of the budget.

An Evaluation of State and Local Rheumatic Fever Programs:

A request has been received from the Rheumatic Fever Committee of the Academy for assistance in a study and evaluation of state and local rheumatic fever programs. The purpose of this study is to provide the background for recommendations for such programs.

Consideration is now being given to the development of such a study with the cooperation not only the Rheumatic Fever Committee of the Academy but also the Council on Rheumatic Fever of the American Heart Association. It should be noted that in any such study of state programs the Academy stands in an almost unique position of effectiveness through its state chairmen.

Publicity:

In the coming months the dissemination of the findings of the national report and the launching of the ICH program require publicity and public relations on the part of one working closely and constantly with the Academy and the ICH Committee. Constant attention must be given to keeping publicity out of the press as well as getting it in; newspapers and the medical profession too, including even those closest to the ICH activities, are wont to arrive at varying and opposite conclusions from a given set of data and recommendations, even with the most careful or preliminary explanations. The releases on the national report therefore when prepared in advance under supervision, and preceded as often as possible by preliminary personal contacts with editors as was done in the case of Dr. Rusk of the New York *Times,* will guarantee a minimum of sensationalism and a maximum of favorable public attention.

It is also deemed essential to the achievement of the Academy's objectives that an active publicity program be maintained to inform the medical profession and the public as to the content and importance of pediatric education as a necessary instrument in bringing better medical care to children. Only as the public recognizes the need for more physicians well trained in the care of children, will ways and means be found to meet the need. Accordingly, Mr. Hiller, a full-time publicity director, has been retained on the staff of the ICH Committee.

Financial Support

In the report of this Committee submitted to the Executive Board on December 7, 1947, a budget of $14,000 was set forth to cover the interim period prior to July 1, 1948 when the staff of the Study Committee would be also serving this Committee. An annual budget of $75,000 was submitted and approved by the Executive Board subject to the procurement of the funds. To meet the requirements ($14,000 plus $75,000) we are pleased to report that to date a total of $79,665 has been received, as shown below. An account of these funds will be found in the Treasurer's report.

Respectfully submitted,

James L. Wilson, M.D., *Chairman*
John P. Hubbard, M.D., *Director*

CONTRIBUTIONS RECEIVED FOR BUDGET OF ICH COMMITTEE

	Received	
American Academy of Pediatrics (Reserve Fund)	$ 5,000	
Academy Fellows—Individual contributions	2,515	
National Foundation for Infantile Paralysis	25,000	($15,000 pledged for 2nd year $10,000 pledged for 3rd year)
Grant Foundation	5,000	
Field Foundation	3,900	
New York Fund for Children, Inc.	3,000	($2,000 pledged for 2nd year $2,000 pledged for 3rd year)
Chas. H. Hood Dairy Foundation	1,000	($1,000 per year pledged for next 4 years)
Carnation Co.	10,000	
Pet Milk Co.	10,000	
M & R Dietetic Laboratory	5,000	
Mead Johnson & Co.	5,000	
Winthrop-Stearns, Inc.	2,500	
Burroughs Welcome	1,000	
C. V. Mosby	500	
Wm. S. Merrill	250	
Total	$79,655	

November 10, 1948

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